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(54) Title: NUCLEIC ACIDS, PROTEINS, AND ANTIBODIES

(57) Abstract: The present invention relates to novel digestive system related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "digestive system antigens", and the use of such digestive system antigens for detecting disorders of the digestive system, particularly the presence of cancer and cancer metastases. More specifically, isolated digestive system associated nucleic acid molecules are provided encoding novel digestive system associated polypeptides. Novel digestive system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human digestive system associated polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the digestive system, including cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



## **Nucleic Acids, Proteins, and Antibodies**

[001] This application refers to a "Sequence Listing" that is provided only on electronic media in computer readable form pursuant to Administrative Instructions Section 801(a)(i). The Sequence Listing forms a part of this description pursuant to Rule 5.2 and Administrative Instructions Sections 801 to 806, and is hereby incorporated in its entirety.

[002] The Sequence Listing is provided as an electronic file (PC002PCT\_seqList.txt, 9,710,493 bytes in size, created on January 12, 2001) on four identical compact discs (CD-R), labeled "COPY 1," "COPY 2," "COPY 3," and "CRF." The Sequence Listing complies with Annex C of the Administrative Instructions, and may be viewed, for example, on an IBM-PC machine running the MS-Windows operating system by using the V viewer software, version 2000 (see World Wide Web URL: <http://www.fileviewer.com>).

### ***Field of the Invention***

[003] The present invention relates to novel digestive system related polynucleotides, the polypeptides encoded by these polynucleotides herein collectively referred to as "digestive system antigens," and antibodies that immunospecifically bind these polypeptides, and the use of such digestive system polynucleotides, antigens, and antibodies for detecting, treating, preventing and/or prognosing disorders of the digestive system, including, but not limited to, the presence of cancer and cancer metastases. More specifically, isolated digestive system nucleic acid molecules are provided encoding novel digestive system polypeptides. Novel digestive system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing

human digestive system polynucleotides, polypeptides, and/or antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the digestive system, including cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The invention further relates to methods and/or compositions for inhibiting or promoting the production and/or function of the polypeptides of the invention.

### ***Background of the Invention***

[004] The Human Digestive System is a collection of specialized organs and body tissues that prepare food for use by hundreds of millions of body cells. Food when eaten cannot reach cells because it cannot pass through the intestinal walls to the bloodstream and, if it could would not be in a useful chemical state. The gut modifies food physically and chemically and disposes of unusable waste. Physical and chemical modification (digestion) depends on exocrine and endocrine secretions and controlled movement of food through the digestive tract.

[005] The three fundamental processes of the Digestive System are: Secretion (e.g., delivery of enzymes, mucus, ions and the like into the lumen, and hormones into blood), Absorption (e.g., transport of water, ions and nutrients from the lumen, across the epithelium and into blood), and Motility (e.g., contractions of smooth muscle in the wall of the tube that crush, mix and propel its contents). Control of digestive function is achieved through a combination of electrical and hormonal messages which originate either within the digestive system's own nervous and endocrine systems, as well as from the central nervous system and from endocrine organs such as the adrenal gland.

[006] The digestive system is composed of the digestive or alimentary tube and accessory digestive organs, which include the Mouth (e.g., tongue, taste buds, soft palate pharynx, salivary glands, teeth), Esophagus, Stomach, Liver, Gallbladder, Pancreas, Small Intestine (e.g., duodenum, jejunum, and ileum), and Large Intestine (e.g., caecum).

- [007] Common digestive system disorders including infections, inflammations, ulcers and cancers of the the digestive or alimentary tube and above listed accessory digestive organs are described in more detail below.

*Disorders of the Esophagus*

- [008] Disorders of the Esophagus include dysphagia (e.g., difficulty in swallowing) and odynophagia (e.g., difficulty in swallowing accompanied by pain). Dysphagia may be prominent in cases of degenerative disease of the central nervous system, especially of the ganglia at the base of the brain. Congenital disorders of the esophagus are most often seen in infancy, primarily as a failure to develop normal passageways. The lower end of the esophagus is subject to various developmental anomalies that shorten the organ so that the stomach is pulled up into the thoracic cavity. Anomalies of the diaphragm may contribute to a similiar outcome. Inflammatory disorders of the esophagus result from a variety of causes; for example, ingestion of noxious materials (e.g., corrosive esophagitis), lodgment of foreign bodies, or a complex of events associated with reflux of gastric contents from the stomach into the lower esophagus (e.g., peptic esophagitis).
- [009] Disorders of the motility of the esophagus tend to be either precipitated or aggravated at times of nervous stress. A disorder commonly due to obesity is gastric reflux. Persisting reflux of gastric contents with acid and digesting enzymes leads to chemical inflammation of the lining of the esophagus and ultimately to (peptic) ulceration. If inadequately treated, the process leads to submucosal fibrosis and stricturing, and, besides the symptoms of heartburn and regurgitation, the patient experiences pain on eating and swallowing.
- [010] Pouches in the walls of the structures in the digestive system that occur wherever weak spots exist between adjacent muscle layers are called diverticula. In the upper esophagus, these may occur in the area where the striated constrictor muscles of the pharynx merge with the smooth muscle of the esophagus just below the larynx. Small diverticula just above the diaphragm sometimes are found after the introduction of surgical instruments into the esophagus. A serious injury to the esophagus is spontaneous rupture. It can occur in patients who have been vomiting or retching and in debilitated elderly persons with chronic lung disease. A rupture of this type confined

to the mucosa only at the junction of the linings of the esophagus and stomach is called a Mallory-Weiss lesion.

- [011] Benign tumors of the esophagus originate in the submucosal tissues and principally are leiomyomas (tumors composed of smooth muscle tissue) or lipomas (tumors composed of adipose, or fat, tissues). Malignant tumors are either epidermal cancers, made up of unorganized aggregates of cells, or adenocarcinomas, in which there are gland-like formations. Cancers arising from squamous tissues are found at all levels of the organ, whereas adenocarcinomas are more common at the lower end where a number of glands of gastric origin are normally present. The prognosis is poor because diagnosis is difficult and the tumor has usually been growing for one or two years before symptoms are apparent.

#### *Disorders of the stomach*

- [012] Any disorder that affects the power of coordination of the stomach muscles is capable of producing symptoms ranging from those that are mildly unpleasant (e.g., anorexia and nausea) to others that are life-threatening. The intrinsic muscles of the stomach are innervated by branches of the vagus nerves, which travel along the esophagus from their point of emergence in the brain stem. Severing these nerves or altering their function by the use of anticholinergic medication may produce temporary or more prolonged change in the ability of the stomach to empty itself. Gastric retention may result from the degeneration of the nerves to the stomach that can result from diabetes mellitus. Obstruction due to scarring in the area of the gastric outlet, or to tumors encroaching on the lumen, causes the stomach to fill up with its own secretions as well as with partially digested food. In these circumstances, vomiting leads to dehydration and to electrolyte losses, which threaten life if not corrected.
- [013] Disorders of the stomach include, ulcerative diseases, which involve mucosal breakdown either confined to the superficial layers of the mucosa (e.g., an erosion) or extending through the intrinsic layer of muscle of the mucosa into the tissues below (e.g., an ulcer). The circumstances that contribute to mucosal injury and ulcer formation include physical and chemical trauma that result from hot fluids and food, aspirin and other drugs, irritating spices, and pickling fluids. In addition, genetic factors are involved in the development of ulcers. The complications of peptic ulcers

are hemorrhage, perforation, and obstruction of the outlet of the stomach (pyloric stenosis) by scarring of the duodenal bulb or of the pyloric channel. A diffuse inflammation of the stomach lining, gastritis, is usually an acute process caused by contaminated food, alcohol abuse, or by bacterial- or viral-induced inflammation of the gastrointestinal tract (gastroenteritis). The other form of gastritis is gastric atrophy, in which the thickness of the mucosa is diminished. Diffuse gastric atrophy leads to partial loss of the glands and secreting cells throughout the stomach and may be associated with iron-deficiency anemia.

- [014] Malignant tumors of the stomach are common and are probably a result of both genetic and environmental factors. Gastric cancer affects men more often than women and accounts for about 20 percent of all deaths from cancers of the gastrointestinal tract in the United States. Other malignant tumors that involve the stomach are tumors ordinarily made up of lymphoid and connective tissue. Benign tumors, especially leiomyomas, are common and may, when large, cause massive hemorrhage. Polyps of the stomach are not common except in the presence of gastric atrophy.

#### *Disorders of the Duodenum and Small Intestine*

- [015] Primary cancer of the duodenum is an infrequent disease, however, benign tumors of the duodenum particularly polyps and carcinoids, are more frequent. Cancers of the common bile duct or of the pancreas are important causes of death. A common disorder of the small intestine, distension, is caused by lack of coordination of the inner circular and outer longitudinal muscular layers of the intestinal wall which usually results in an accumulation of excess contents in the lumen. The most common cause of disturbed motility in the small intestine is food that contains an unsuitable additive, organism, or component. One of the most serious problems in small intestine are motor disturbances which arise from an intestinal obstruction that results from an actual encroachment on the bowel by an adhesive band or from an internal block produced by a tumor or gallstone. In addition, as profound an obstruction results when a portion of the intestine undergoes partial necrosis, or death, from failure of its blood supply.

- [016] The extremely common disorder known as the irritable bowel syndrome is probably due to a disturbance of the motility of the whole intestinal tract. The

symptoms vary from watery diarrhea to constipation and the passage of stools with difficulty. When the colon is involved, an excess of mucus is often observed in the stools. Occasionally the irritable bowel syndrome may be due to an allergy to a particular foodstuff. The syndrome may develop following an infection such as bacillary dysentery, after which the small intestine remains irritable for many months.

[017] A further disorder, malabsorption occurs when the small intestine is unable to transport properly broken down products of digestive materials from the lumen of the intestine into the lymphatics or mesenteric veins, where they are distributed to the rest of the body. Defects in transport occur either because the absorptive cells of the intestine lack certain enzymes, whether by birth defect or by acquired disease, or because they are hindered in their work by other disease processes that infiltrate the tissues, disturb motility, permit bacteria to overpopulate the bowel, or block the pathways over which transport normally proceeds. A malabsorption disorder of unknown cause, tropical sprue, is associated with partial atrophy of the mucosa of the small intestine.

[018] Several disorders of the small intestine are congenital. For example, Meckel's diverticulum is a common congenital malformation that occurs when the duct leading from the navel to the small intestine in the fetus fails to atrophy and close. Another congenital problem in the small intestine is the presence of multiple diverticula, or outpouchings of mucosa and serosa. A third congenital malformation is a failure of complete rotation of the small and large intestine, which is a normal step in the development of the fetus. This can result in abnormal intestinal attachments with a subsequent risk of obstruction when the intestine twists around the attachments.

[019] Disorders of the small intestine also include bacterial and parasitic infections. Traveler's diarrhea (e.g., diarrhea which is watery, accompanied by cramps, and lasts a few days) is most often caused by toxin-generating *Escherichia coli*, and less often by other organisms. Such diarrhea generally disappears spontaneously with abstention from food accompanied by drinking of nonalcoholic fluids. Species of *Salmonella* that cause typhoid and paratyphoid remain endemic in some countries and, together with *Shigella*, are occasional causes of epidemics in institutions. Cholera, caused by *Vibrio cholerae*, is endemic to Southeast Asia and periodically becomes pandemic. In equatorial countries, parasitism is endemic, with Roundworms, tapeworms, amoebae,

hookworms, strongyloides, threadworms, and blood flukes (schistosomiasis) being the main types of parasites. Roundworms, or *Ascariasis lumbricoides* interfere with the absorption of fat and protein in the intestine, which causes diarrhea. Hookworm, or *Ancylostoma duodenale*, infection deplete the body of nutrients, and a major effect is severe chronic iron-deficiency anemia. Threadworms, or *Enterobius vermicularis*, live mainly in the cecum and cause anal itching. Common tapeworms are *Taenia saginata*, found in beef, and *T. solium*, found in pork. Larvae of *Echinococcus granulosus*, *Diphyllobothrium* species, and some dwarf tapeworms also cause disease. Tapeworms found in beef and pork only give rise to symptoms if their number and size cause intestinal obstruction. *Diphyllobothrium latum*, a fish tapeworm, may cause a severe anemia similar to pernicious anemia, because it consumes most of the vitamin in the diet of the host.

[020] Appendicitis is an inflammation of the vermiform appendix that may be caused by infection or partial or total obstruction. Chronic inflammations of the small intestine include tuberculosis and regional enteritis (Crohn's disease). Celiac disease causes damage to the mucosa of the small intestine, though it is not clear whether it is caused by an immune reaction, or an inability to break down a toxic protein, gluten, to smaller peptide fractions. Studies of the immune function of those with celiac disease suggest that at least a major part of the process is a delayed hypersensitivity reaction and that the morphological changes are correlated with the presence of circulating antibodies to gluten. The mucosal reaction results in progressive atrophy, with dwarfing, if not complete disappearance, of the microvilli and villi that line the intestinal tract.

#### *Disorders of the Large Intestine*

[021] A wide variety of diseases and disorders occur in the large intestine. Imperfect fetal development may result in an anus that has no opening, a defect that requires major plastic surgery to correct. Abnormal rotation of the colon is fairly frequent and occasionally leads to disorders. Unusually long mesenteries (the supporting tissues of the large intestine) may permit recurrent twisting, cutting off the blood supply to the involved loop. Brain disease, metabolic failure, or drugs can dull the normal signals that give rise to the urge to defecate. Poor abdominal musculature or a poor pelvic floor makes it difficult to mobilize effective pressures to bring about defecation.



[022] A disease that is analogous to achalasia of the esophagus is an idiopathic condition called aganglionic megacolon, or Hirschsprung's disease. It is characterized by the absence of ganglion cells and normal nerve fibres from the distal (or lower) portion of the large intestine, which results in reduced neuromuscular transmission and ceased peristalsis. The entire colon slowly becomes more and more distended and thick-walled. A related disorder, acquired megacolon, is commonly caused by a combination of faulty toilet training and emotional disorders during childhood, in which the child withholds defecation. This starts a cycle of the administration of increasing amounts of laxatives with, ultimately, damage to the intrinsic innervation in the intestinal wall. A huge, dilated rectum full of feces develops over the years and act as an obstruction, leading to voluminous dilatation of the whole colon in some cases. The same phenomenon is occasionally encountered in those with schizophrenia and severe depression.

[023] Abscesses in the perianal area are common complicating features of many diseases and disorders of the large intestine. Fungal and bacterial infections are also common causes of large intestine disorders. Fungal infections of the moist and poorly cleansed area around the anus permit the maceration of tissue and the invasion by bacteria from the skin and colon. The colon may become inflamed and ulcerate because of invasion by pathogenic, or disease-causing, bacteria or parasites, or viral infection. For example, *Shigella* species may attack the mucous membrane of the colon and produce an intense but rather superficial hemorrhage; *Salmonella* species may damage the lymph follicles of the colon, but do not produce a generalized inflammation of the colon; cytomegalic virus can cause a severe colitis producing ulcerations; *Lymphopathia venereum* can cause a more generalized and superficial colitis; and *Entamoeba histolytica* lodge in the cecum and ascending colon, undermine the mucosal coat, and may create large ulcerations that bleed impressively.

[024] The most common form of chronic colitis, ulcerative colitis, is idiopathic. It varies from a mild inflammation of the mucosa of the rectum, giving rise to excessive mucus and some spotting of blood in the stools, to a severe, sudden, intense illness, with destruction of a large part of the colonic mucosa, considerable blood loss, toxemia and, less commonly, perforation. The most common variety affects only the rectum and sigmoid colon and is characterized by diarrhea and the passage of mucus.

Apart from the greater tendency for fistulas to form and for the wall of the intestine to thicken until the channel is obstructed, Crohn's disease is distinguishable from ulcerative colitis by microscopic findings. In Crohn's disease, the maximum damage occurs beneath the mucosa, and lymphoid conglomerations, known as granulomata, are formed in the submucosa. Crohn's disease attacks the perianal tissues more often than does ulcerative colitis. Although these two diseases are not common, they are disabling.

[025] Tumors of the colon are usually polyps or cancers. A peculiar form of polyp is the villous adenoma, often a slowly growing, fernlike structure that spreads along the surface of the colon for some distance. In the West, cancer of the colon is a more common tumor than is cancer of the stomach, and it occurs about equally in both sexes. Cancers compress the colonic lumen to produce obstruction, they attach to neighbouring structures to produce pain, and they perforate to give rise to peritonitis. Cancers also may metastasize to distant organs before local symptoms appear.

[026] Anorectal disorders related to defecation are more common in the Western world than elsewhere. These disorders usually take the form of fissures (cuts or cracks in the skin or mucous membrane) at the junction of the anal mucous membrane with the skin between the thighs. Anal fistulas sometimes occur as complications of serious bowel disease, as in tuberculosis or Crohn's disease of the bowel, or in certain parasitic diseases. A more general disorder is the enlargement of veins of the rectum and anus to form external or internal hemorrhoids. Hemorrhoids protrude, are associated with anal itching and pain, and bleed, especially when they come in contact with hard stools.

#### *Disorders of the Liver*

[027] A variety of agents, including viruses, drugs, environmental pollutants, genetic disorders, and systemic diseases, can affect the liver. The resulting disorders usually affect one of the three functional components of the liver: the hepatocyte (liver cell) itself, the bile secretory (cholangiolar) apparatus, or the blood vascular system. Most acute liver diseases are self-limited, and liver functioning returns to normal once the causes are removed or eliminated. In some cases, however, the acute disease process destroys massive areas of liver tissue in a short time, leading to extensive death

(necrosis) of hepatic cells and often to death of the patient. Hepatitis may result from viral infections or toxic damage from drugs or poisons. When acute hepatitis lasts for six months or more, a slow but progressive destruction of the surrounding liver cells and bile ducts occurs, a stage called chronic active hepatitis. If hepatocellular damage is severe enough to destroy entire acini (clusters of lobules), they are often replaced with fibrous scar tissue. Bile canaliculi and hepatocytes regenerate in an irregular fashion adjacent to the scar tissue and result in a chronic condition called cirrhosis of the liver. Where inflammatory activity continues after the onset of cirrhosis, the disorderly regeneration of hepatocytes and cholangioles may lead to the development of hepatocellular or cholangiolar cancer.

[028] Although a number of viruses affect the liver, including the cytomegalovirus of infancy and childhood and the Epstein-Barr virus of infectious mononucleosis, there are three distinctive transmissible viruses that are specifically known to cause acute damage to liver cells: hepatitis virus A (HAV), hepatitis virus B (HBV), and hepatitis virus non-A, non-B (NANB). The hepatitis A virus is transmitted almost exclusively by the fecal-oral route, and it thrives in areas where sanitation and food handling are poor and hand washing is infrequent. Hepatitis B virus is present throughout the world in asymptomatic human carriers who may or may not have ongoing liver disease and formerly, the disease was widely spread by the transfusion of whole blood or blood products. The hepatitis NANB virus has not been isolated, and currently is the major cause of posttransfusion hepatitis. The symptoms characteristic of the acute hepatitis caused by the HAV, HBV, and NANB viruses are essentially indistinguishable from one another.

[029] Acute hepatitis also may be caused by the overconsumption of alcohol or other poisons, such as commercial solvents (e.g., carbon tetrachloride), acetaminophen, and certain fungi. Such agents are believed to cause hepatitis when the formation of their toxic intermediate metabolites in the liver cell (phase I reactions) is beyond the capacity of the hepatocyte to conjugate, or join them with another substance for detoxification (phase II reactions) and excretion. As long as the levels of these agents are small enough to permit complete phase I and phase II reactions, there is no damage to the liver cell. Acute canalicular (cholestatic) hepatitis is most commonly caused by certain drugs, such as chlorpromazine, that lead to idiosyncratic reactions or, at times,

by hepatitis viruses. Acute congestive liver disease usually results from the sudden engorgement of the liver by fluids after congestive heart failure.

[030] Chronic active hepatitis, the result of unresolved acute injury, is associated with ongoing liver damage. A milder form of chronic disease, called persistent hepatitis, does not appear to lead to progressive liver damage despite evidence of a continuing mild inflammation. These conditions may result from viral hepatitis, drug-induced hepatitis, autoimmune liver diseases (lupoid hepatitis), or congenital abnormalities. A prominent autoimmune liver disease is Wilson's disease, which is caused by abnormal deposits of large amounts of copper in the liver. Granulomatous hepatitis, a condition in which localized areas of inflammation (granulomas) appear in any portion of the liver lobule, is a type of inflammatory disorder associated with many systemic diseases, including tuberculosis, sarcoidosis, schistosomiasis, and certain drug reactions. Granulomatous hepatitis rarely leads to serious interference with hepatic function, although it is often chronic.

[031] The end result of many forms of chronic liver injury is cirrhosis, or scarring of liver tissue in response to previous acinar necrosis and irregular regeneration of liver nodules and bile ducts. Among the congenital disorders producing cirrhosis are Wilson's disease, hemochromatosis (over-deposition of iron pigment), cystic fibrosis, biliary atresia (congenital absence of a part of the bile ducts), and alpha1-antitrypsin deficiency, or the congenital absence of a proteolytic enzyme inhibitor that results in the accumulation of abnormal forms of carbohydrate in hepatocytes. In the West, cirrhosis of the liver most commonly results from chronic heavy intake of alcohol, while chronic viral hepatitis is probably the leading cause of cirrhosis in underdeveloped countries. Primary biliary cirrhosis, a widespread, though uncommon, autoimmune inflammatory disease of bile ducts, is a disorder primarily affecting middle-aged and older women. Secondary biliary cirrhosis results from chronic obstruction or recurrent infection in the extrahepatic bile ducts caused by strictures, gallstones, or tumors. Infestation of the biliary tract with a liver fluke, *Clonorchis sinensis*, is a cause of secondary biliary cirrhosis in Asia. Cirrhosis occasionally is the result of chronic vascular congestion of the liver in persons with prolonged heart failure and in those with chronic obstruction of the hepatic veins caused by benign blood clots or metastatic cancer.

[032] Hepatic encephalopathy refers to the changes in the brain that occur in patients with advanced acute or chronic liver disease. If liver cells are damaged, certain substances that are normally cleansed from the blood by the healthy liver are not removed. In the case of cirrhosis, blood from the portal system is not exposed to functioning hepatocytes because it is transported through blood vessels in the liver that do not run through regenerating nodules of hepatocytes; owing to the atypical growth inherent in the cirrhotic process. These products of cell metabolism are primarily nitrogenous substances derived from protein, especially ammonia, or possibly certain straight-chain fatty acids. They pass to the brain where they damage functioning nervous tissue or subvert the actions of neurotransmitters, chemical messengers that carry impulses from one brain cell to another. In acute diseases, the brain exposed to those agents becomes swollen to the point where normal breathing may cease. Chronic exposure can lead to destruction of nerve cells with replacement by scar tissue (gliosis).

[033] Portal hypertension, the increased pressure in the portal vein and its tributaries that is the result of impediments to venous flow into the liver, is brought about by the scarring characteristic of the cirrhotic process. The increased pressure causes feeders of the portal vein to distend markedly, producing varices, or dilations of the veins. When varices are located in superficial tissues, they may rupture and bleed profusely. Two such locations are the lower esophagus and the perianal region. The accumulation of fluid in the abdominal cavity, or ascites, is related to portal hypertension, significant reduction in serum albumin, and renal retention of sodium. When albumin levels in blood are lower than normal, there is a marked reduction in the force that holds plasma water within the blood vessels and normally resists the effects of the intravascular pressure. The resulting increase in intravascular pressure, coupled with the increased internal pressure caused by the portal venous obstruction in the liver, leads to massive losses of plasma water into the abdominal cavity. The associated reduction of blood flow to the kidneys causes increased elaboration of the hormone aldosterone, which, in turn, causes the retention of sodium and water and a reduction in urinary output. In addition, because the movement of intestinal lymph into the liver is blocked by the cirrhotic process in the liver, the backflow of this fluid into the abdominal cavity is greatly increased. A progressive reduction in kidney function that often occurs in

persons with advanced acute or chronic liver disease, hepatorenal syndrome, probably results from an inadequate perfusion of blood through the cortical (outer) portions of the kidneys, where most removal of waste products occurs. With advanced hepatocytic dysfunction, a spasm of blood vessels in the renal cortex can occur, often with good blood flow to the rest of the kidney. This spasm results in progressive failure in kidney function and often leads to death.

- [034] Although not uncommon, cancer originating in the liver, usually in hepatocytes and less frequently in cells of bile duct origin, is rare in the West and is almost always associated with active cirrhosis, particularly the form found in patients with chronic hepatitis. The survival rate from liver cancer is small. In certain underdeveloped countries, especially in tribal Africa, the incidence of this malignancy is high and is a major cause of death in the population. Most of these cases appear to stem from the prevalence of chronic viral hepatitis or the chronic presence of viruses in the blood (viremia) caused by hepatitis B. Long exposure to certain environmental poisons, such as vinyl chloride or carbon tetrachloride, has also been shown to lead to hepatic cancer. Cancers arising elsewhere in the body, particularly in abdominal organs, lungs, and lymphoid tissue, commonly lead to metastatic cancer in the liver and are by far the most frequent type of hepatic malignancy. Various benign types of tumors and cysts arise from certain components of the liver, such as the hepatocytes (adenomas) or blood vessels (hemangiomas). While the cause of these lesions is not always clear, hepatic adenomas are associated with the prolonged use of female sex hormones (estrogens). Benign cysts in the liver may occur as congenital defects or as the result of infections from infestation of the dog tapeworm (*Echinococcus granulosus*). Abscesses on the liver result from the spread of infection from the biliary tract or from other parts of the body, especially the appendix and the pelvic organs. Specific liver abscesses also result from infections with the intestinal parasite *Entamoeba histolytica*.

#### *Disorders of the Biliary Tract*

- [035] Cholelithiasis, or the formation of gallstones in the gallbladder, is the most common disease of the biliary tract. There are three types of Gallstones: stones containing primarily calcium bilirubinate (pigment stones); stones containing 25 percent or more of cholesterol; and stones composed of variable mixtures of both

bilirubin and cholesterol (mixed gallstones). Pigment stones are the result of an increased amount of bilirubin in the liver (due to hemolytic disease) and the consequent secretion into the biliary tract of increased amounts of the water-soluble conjugate, bilirubin diglucuronide, a pigment that is normally secreted in the urine. In the biliary tract, particularly in the gallbladder, some of this bilirubin diglucuronide is broken down by bacterial or mucosal enzymes into water-insoluble bilirubin, which then tends to form stones. Cholesterol and mixed cholesterol-bilirubinate stones occur when the proportion of cholesterol in bile exceeds the capacity of bile acids and lecithin to contain the total amount of cholesterol in micellar colloidal solution. When this critical micellar concentration is surpassed and the solution is saturated, crystalline particles of cholesterol are formed. The resulting gallstones contain large amounts of crystalline cholesterol and smaller quantities of calcium bilirubinate. Postcholecystectomy syndrome comprises painful attacks, often resembling preoperative symptoms, that occasionally occur following the surgical removal of gallstones and the gallbladder. These attacks may be related to intermittent muscular spasms of the sphincter of Oddi or of the bile ducts.

[036] Cancer of the biliary tract is rare but may occur in almost any area, including the gallbladder, the hepatic ducts, the common bile duct, or the ampulla of Vater. In cancer of the bile duct, congenital cysts and parasitic infections, such as liver flukes, seem to lead to increased risks. Persons with extensive chronic ulcerative colitis also show a greater than normal incidence of bile duct carcinoma.

[037] Jaundice, or yellowing of the skin, scleras, and mucous membranes, occurs whenever the level of bilirubin in the blood is significantly above normal. This condition is evident in three different types of disorders including, unconjugated, or hemolytic, jaundice; hepatocellular jaundice; and cholestatic, or obstructive jaundice. Unconjugated jaundice results when the amount of bilirubin produced from hemoglobin by the destruction of red blood cells or muscle tissue (myoglobin) overwhelms the normal capacity of the liver to transport it or when the ability of the liver to conjugate normal amounts of bilirubin into bilirubin diglucuronide is significantly reduced by inadequate intracellular transport or enzyme systems. Hepatocellular jaundice arises when liver cells are damaged so severely that their ability to transport bilirubin diglucuronide into the biliary system is reduced, allowing



some of this yellow pigment to regurgitate into the bloodstream. Cholestatic jaundice, occurs when essentially normal liver cells are unable to transport bilirubin either through the hepatocytic-bile capillary membrane, because of damage in that area, or through the biliary tract, because of anatomical obstructions (e.g., atresias, gallstones, cancer).

#### *Disorders of the Pancreas*

[038] Inflammation of the pancreas, or pancreatitis, is probably the most common disease of this organ. The disorder may be confined to either singular or repeated acute episodes, or it may become a chronic disease. There are many factors associated with the onset of pancreatitis, including direct injury, certain drugs, viral infections, heredity, hyperlipidemia (increased levels of blood fats), and congenital derangements of the ductal system. Localized, severe abdominal and midback pain resulting from enzyme leakage, tissue damage, and nerve irritation is the most common symptom of acute pancreatitis. In severe cases, respiratory failure, shock, and even death may occur. Chronic pancreatitis rarely follows repeated acute attacks. It seems instead to be a separate disorder that results in mucus plugs and precipitation of calcium salts in the smaller pancreatic ducts. Cystic fibrosis is inherited, but it is not expressed unless both members of a pair of homologous, or corresponding, chromosomes carry the trait. The major functional abnormality in persons with the disease appears to be the elaboration by mucous glands throughout the body of secretions containing greater than normal concentrations of protein and calcium. This imbalance leads to increased viscosity of the secretions and precipitation of mucus and organic constituents in gland ducts. The resulting plugging process in the pancreas almost invariably causes destruction and scarring of the acinar tissue, usually without damaging the islets of Langerhans. A similar process in the hepatic biliary system produces foci of fibrosis and bile duct proliferation, a singular form of cirrhosis.

[039] The discovery of new human digestive system associated polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, prevention and/or prognosis of disorders of the digestive system, including, but not limited to, dysphagia, odynophagia, congenital

disorders of the esophagus, gastric reflux, diverticula, Mallory-Weiss lesions, leiomyomas of the esophagus, lipoma, anorexia, nausea, ulcerative disease, pyloric stenosis, gastroenteritis, gastritis, gastric atrophy, gastric cancer, benign tumors of the duodenum (e.g., polyps and carcinoids), pancreatic cancer, cancer of the bile duct, distension, irritable bowel syndrome, malabsorption, congenital disorders of the small intestine (e.g., Meckel's diverticulum, multiple diverticula), bacterial and parasitic infection (e.g., traveler's diarrhea, typhoid, paratyphoid, cholera, roundworms, tapeworms, amoebae, hookworms, strongyloides, threadworms, and blood flukes), megacolon (e.g., Hirschsprung's disease, aganglionic megacolon, acquired megacolon), colitis (e.g., due to bacterial, fungal, or parasitic infection, ulcerative colitis), tumors of the colon (e.g., polyps or cancers), anorectal disorders (e.g., anal fistulas, hemorrhoids, hepatitis (e.g., acute, chronic, persistent hepatitis, viral (for example, hepatitis caused by hepatitis virus A (HAV), hepatitis virus B (HBV), and hepatitis virus non-A, non-B (NANB) infection), congenital disorders of the liver (e.g., Wilson's disease, hemochromatosis, cystic fibrosis, biliary atresia, and alpha-1 antitrypsin deficiency), cirrhosis, portal hypertension, cholelithiasis, cancer of the biliary tract, jaundice (e.g., unconjugated, hemolytic, hepatocellular, cholestatic, or obstructive jaundice).

### *Summary of the Invention*

[040] The present invention relates to novel digestive system related polynucleotides, the polypeptides encoded by these polynucleotides herein collectively referred to as "digestive system antigens," and antibodies that immunospecifically bind these polypeptides, and the use of such digestive system polynucleotides, antigens, and antibodies for detecting, treating, preventing and/or prognosing disorders of the digestive system, including, but not limited to, the presence of cancer and cancer metastases. More specifically, isolated digestive system nucleic acid molecules are provided encoding novel digestive system polypeptides. Novel digestive system polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human digestive system polynucleotides, polypeptides, and/or antibodies. The

invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the digestive system, including cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The invention further relates to methods and/or compositions for inhibiting or promoting the production and/or function of the polypeptides of the invention.

### *Detailed Description*

#### Tables

[041] Table 1A summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA plasmid related to each digestive system associated contig sequence disclosed in Table 1A. The second column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for each of the contig polynucleotide sequences disclosed in Table 1A. The fourth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1A as SEQ ID NO:Y (column 5). Column 6 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4:181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids

are indicated in Table 1A as "Predicted Epitopes." In particular embodiments, digestive system associated polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1A. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 7, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 7 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 7 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of  $^{33}\text{P}$  dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides

which show predominant and/or specific tissue and/or cell expression. Column 8, "Cytologic Band," provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlapped with the chromosomal location of a Morbid Map entry, an OMIM identification number is provided in Table 1A, column 9 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

[042] Table 1B summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

[043] Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1A and allowing for correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the row was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of PFAM/NR hits having significant matches to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in column five. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by the polynucleotides in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[044] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to digestive system associated contig sequences disclosed in Table 1A. The second column provides the sequence identifier, "SEQ ID NO:X", for contig polynucleotide sequences disclosed in Table 1A. The third column provides the unique contig identifier, "Contig ID", for contigs disclosed in Table 1A. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, represented as "Range of a", and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, represented as "Range of b", where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the

polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the polynucleotides of the invention (including polynucleotide fragments and variants as described herein and diagnostic and/or therapeutic uses based on these polynucleotides) are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

[045] Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1A, column 7. Column 1 provides the key to the tissue/cell source identifier code disclosed in Table 1A, Column 7. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[046] Table 5 provides a key to the OMIM™ reference identification numbers disclosed in Table 1A, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 1A, column 8, as determined from the Morbid Map



database.

[047] Table 6 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

[048] Table 7 shows the cDNA libraries sequenced, tissue source description, vector information and ATCC designation numbers relating to these cDNA libraries.

[049] Table 8 provides a physical characterization of clones encompassed by the invention. The first column provides the unique clone identifier, "Clone ID NO:Z", for certain cDNA clones of the invention, as described in Table 1A. The second column provides the size of the cDNA insert contained in the corresponding cDNA clone.

### **Definitions**

[050] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[051] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide sequences of the present invention.

[052] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof, a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1A) or the complement thereof, a cDNA sequence contained in Clone ID NO:Z (as described in column 1 of Table 1A and contained within a library deposited with the ATCC); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment or variant thereof; or

a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[053] As used herein, a "digestive system antigen" refers collectively to any polynucleotide disclosed herein (e.g., a nucleic acid sequence contained in SEQ ID NO:X or the complement thereof, or cDNA sequence contained in Clone ID NO:Z, or a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereof and fragments or variants thereof as described herein) or any polypeptide disclosed herein (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, or the complement thereof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z, an amino acid sequence encoded by SEQ ID NO:B, or the complement thereof, and fragments or variants thereof as described herein). These digestive system antigens have been determined to be predominantly expressed in digestive system tissues, including normal or diseased tissues (as shown in Table 1A column 7 and Table 4).

[054] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 1 of Table 1A, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, certain clones disclosed in this application have been deposited with the ATCC on October 5, 2000, having the ATCC

designation numbers PTA 2574 and PTA 2575; and on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID NO:Z to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID NO:Z) isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1A correlates the Clone ID NO:Z names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1A, 6 and 7 to determine the corresponding Clone ID NO:Z, which library it came from and which ATCC deposit the library is contained in. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[055] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[056] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any

one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCC, described herein) and/or the polynucleotide sequence delineated in column 6 of Table 1B or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[057] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency), salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[058] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[059] Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of

"polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[060] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[061] The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent

attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992).)

[062] "SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1A or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 5 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 3 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 1 of Table 1A.

[063] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[064] Table 1A summarizes some of the digestive system associated polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and

clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

### **Polynucleotides and Polypeptides**

#### **TABLE 1A**



Clone ID NO: Z	Contig ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Tissue Distribution Library code: count (see Table IV for Library Codes)	Cytologic Band	OMIM Disease Reference(s):
H2CBG54	893910	11	3 - 641	1271	Ser-18 to Val-29, His-45 to Leu-51, Pro-86 to Lys-102, Glu-123 to Tyr-129, Leu-156 to Cys-161.	L0005: 1, T0110: 1, H0039: 1 and L0596: 1.		
H2MBV93	686344	12	98 - 352	1272	Arg-1 to Ser-6.	T0109: 1 and H0539: 1.		
HALSC22	503082	13	67 - 336	1273		H0098: 2		
HALSE71	509638	14	53 - 145	1274		H0098: 2		
HALSG01	500834	15	110 - 256	1275	Leu-8 to Tyr-15, Gly-24 to Thr-29.	H0098: 2		
HALSH86	501004	16	3 - 104	1276		H0098: 2		
HALSJ15	501008	17	167 - 268	1277		H0098: 2		
HALSK15	501003	18	442 - 579	1278	Lys-11 to Arg-21.	H0574: 3, L0748: 2, H0098: 1 and H0014: 1.	6p21.3	106300, 108800, 120290, 120290, 120810, 120820, 142857, 142858, 150270, 167250,

								170261, 177900, 179450, 201910, 217000, 222100, 233100, 235200, 248611, 256550, 256550, 600202, 600261, 601868, 602280, 602475
HALSL45	723542	19	220 - 396	1279	Leu-24 to Thr-29, Thr-47 to Tyr-56.	L0756: 3, L0517: 2, H0098: 1, H0510: 1 and L0731: 1.		
HALSN27	509759	20	145 - 318	1280	Lys-1 to Ser-6, Trp-35 to Asp-47.	H0098: 2.		
HALSN49	971590	21	1 - 75	1281		H0098: 2		
HBAAE56	953244	22	1 - 165	1282		S0356: 1, S0410: 1 and S0404: 1.		
HBAAF58	861603	23	237 - 425	1283	Asp-8 to Leu-16.	S0404: 2		
HCLHD88	929223	24	1 - 339	1284	Ser-9 to Trp-18, Pro-33 to Arg-44.	H0676: 2		
HCNAC10	968738	25	15 - 167	1285		H0085: 2		

HCNAG07	954493	26	2 - 157	1286			H0085: 2 and H0597: 1.		
HCNAK56	832249	27	1 - 99	1287			H0085: 1 and H0231: 1.		
HCNAL66	832247	28	437 - 180	1288			H0085: 1, H0597: 1, L0775: 1 and L0748: 1.		
HCNAN69	655816	29	1 - 318	1289	Pro-28 to Arg-34, Cys-40 to Arg-45, Pro-49 to Asp-56.		H0085: 2		
HCNAO20	832251	30	69 - 314	1290	Phe-24 to Thr-36, Pro-60 to Thr-70.		H0085: 2, L0748: 2 and H0597: 1.		
HCNAR21	948746	31	68 - 154	1291	Arg-1 to Ile-6.		H0085: 2		
HCNAX26	832250	32	64 - 216	1292	Arg-23 to Ser-30.		H0085: 1 and H0597: 1.		
HCNCF73	762056	33	13 - 291	1293	Tyr-54 to Lys-59.		H0597: 2		
HCNCH64	922009	34	3 - 311	1294			H0597: 2		
HCNCN84	766990	35	1 - 270	1295	Pro-59 to Pro-66.		H0597: 2		
HCNCQ46	832349	36	1 - 183	1296	Pro-5 to Gly-13, Gly-31 to Gly-38, Pro-46 to Lys-57.		H0597: 2 and H0595: 1.		
HCNCQ79	832242	37	118 - 2	1297			H0085: 1 and H0597: 1.		
HCNCQ81	887923	38	3 - 131	1298			H0574: 1 and H0597: 1.		
HCNCU02	918993	39	2 - 265	1299	Arg-1 to Lys-14, Arg-19 to Pro-27.		H0597: 2		
HCNCU83	731739	40	350 - 496	1300			H0597: 1 and		

HCNCV19	832221	41	59 - 193	1301	Lys-14 to Ile-19.	H0510: 1.		
HCNCY39	960373	42	2 - 151	1302	Thr-1 to Asn-10.	H0085: 1 and H0597: 1.		
HCNDB53	832225	43	7 - 177	1303	Gly-26 to Gln-31.	H0597: 1 and H0231: 1.		
HCNDD83	832230	44	116 - 271	1304		H0085: 1 and H0597: 1.		
HCNDF20	669111	45	258 - 46	1305		H0597: 1 and H0231: 1.		
HCNDG69	666726	46	134 - 295	1306		H0597: 2		
HCNDH18	832215	47	2 - 202	1307		H0597: 2		
HCNDI01	832213	48	116 - 286	1308		H0085: 1 and H0597: 1.		
HCNDK62	742883	49	17 - 412	1309		H0597: 1 and H0014: 1.		
HCNDL91	832209	50	54 - 260	1310		S0358: 1 and H0597: 1.		
HCNDN43	832212	51	85 - 291	1311		H0597: 1 and H0231: 1.		
HCNDQ50	723976	52	106 - 234	1312		H0597: 2		
HCNDV42	927262	53	26 - 151	1313		H0597: 2		
HCNSM15	914484	54	2 - 289	1314	Pro-39 to Ser-47.	S0354: 1, H0231: 1 and L0740: 1.		
HCNSP37	655829	55	120 - 260	1315	Leu-12 to His-23.	H0231: 2		
HCNSQ03	832200	56	53 - 205	1316	Lys-33 to Pro-41.	S0354: 1 and H0231: 1.		

HCNUA60	695786	57	15 - 245	1317	Arg-5 to Arg-15.	AR089: 4, AR061: 2 H0232: 2 H0232: 2		
HCNUA84	522523	58	3 - 194	1318				
HCQAK31	915563	59	998 - 1192	1319	Ser-33 to Pro-44.	L0770: 3, L0764: 3, L0773: 3, H0596: 2, L0771: 2, L0805: 2, S0360: 1, S0408: 1, H0263: 1, S0464: 1, L0772: 1, L0646: 1, L0375: 1 and L0758: 1.	Xq22	300088, 300300, 300300, 301201, 301500, 301835, 303630, 303630, 303631, 304500, 304700, 304700, 304700, 309300, 309605, 311850, 312080, 312080
HCQCR67	974592	60	1 - 252	1320	Pro-49 to Leu-55.	H0596: 3		
HCRMC26	913972	61	472 - 158	1321	Val-1 to Pro-25.	S0356: 2 and L0658: 1.		
HCRMJ47	919757	62	112 - 537	1322	Asn-3 to Trp-18, Gly-30 to Ser-35, Pro-41 to Ser-51, Pro-87 to Pro-100,	S0356: 2	4p16.3	134934, 134934, 134934, 134934,

						Gly-102 to Gly-108.				134934, 143100, 180072, 180072, 194190, 252800, 252800, 252800, 600965
HCRMP18	888719	63	3 - 623	1323		Pro-111 to Arg-117, Pro-122 to Glu-130.		S0356: 2		
HCRMR08	958489	64	349 - 513	1324				S0356: 2		
HCRMR69	877118	65	2 - 331	1325		Ala-31 to Ser-36, Gln-42 to Gly-49.		AR089: 30, AR061: 10 S0356: 1 and H0622: 1.		
HCRMT41	974324	66	1 - 630	1326				S0356: 3		
HCRND67	921398	67	2011 - 1673	1327				S0356: 3		
HCRNF63	916063	68	201 - 1	1328		Gly-10 to Thr-15.		S0356: 2 and L0777: 1.		
HCRNH81	914840	69	3 - 638	1329				S0356: 1 and H0622: 1.		
HCRNI04	849408	70	202 - 405	1330		Leu-53 to Gly-58.		S0356: 3 and L0747: 2.		
HCRNK95	890458	71	87 - 242	1331				S0356: 2	1	
HCROE42	950701	72	3 - 683	1332		Phe-48 to Gly-56, Ile-60 to Glu-65, Pro-73 to Trp-80,		L0805: 2, S0356: 1, H0596: 1 and S0350: 1.	17q	

HCROM08	974135	73				Ser-100 to Gly-112.				
HCRON75	922386	74	1 - 204	1333		Cys-1 to Gly-6.	S0356: 3			
HCROV23	975245	75	3 - 200	1334		Val-20 to Asn-27.	S0356: 2	4		
			324 - 644	1335		Pro-8 to Glu-17, Arg-24 to Arg-31, Leu-39 to Pro-49, Val-65 to Met-73.	S0356: 4			
HCROZ66	909686	76	239 - 391	1336		Arg-7 to Lys-13.	S0356: 2			
HCRPT92	931152	77	2 - 907	1337		Pro-40 to Gly-47, Gly-63 to Leu-68, Asn-82 to Asp-87, Asn-101 to Glu-106, Ala-162 to Asp-168, Ser-194 to Ser-204.	AR089: 7, AR061: 5 S0328: 2 and S0356: 1.			
HCRPU05	931081	78	1 - 267	1338		Ser-6 to Phe-19, Thr-31 to Lys-58, Gly-73 to Met-81.	S0356: 2			
HCRPZ11	973908	79	635 - 399	1339			S0356: 3			
HCRQG35	954968	80	290 - 502	1340		Glu-1 to Tyr-6.	S0356: 1, S0376: 1 and L0752: 1.			
HDDAD23	967714	81	2 - 211	1341		Thr-27 to Met-34, Arg-60 to Lys-66.	H0339: 2			
HDDAF44	715802	82	375 - 563	1342			L0623: 2, S0360: 1, H0339: 1, L0622: 1, L0774: 1, L0743: 1, L0748: 1, L0754: 1, L0747: 1, L0750: 1 and L0779: 1.	16q22-q23	103850, 114835, 121360, 217800, 218030	

HDRMA28	841936	83	47 - 298	1343	Glu-54 to Ala-61, Pro-63 to Ala-82.	S0352: 2		
HDRMB41	691662	84	203 - 51	1344	Lys-1 to Asn-6, Pro-12 to Thr-21, Glu-30 to Phe-51.	S0352: 2		
HDRME31	697523	85	225 - 392	1345		S0352: 2		
HDRMF01	915726	86	1 - 129	1346	Leu-24 to Asp-31.	H0014: 1 and S0352: 1.		
HEPND10	963559	87	368 - 625	1347	His-4 to Leu-9, Tyr-24 to Asp-29, Arg-58 to Arg-65.	S0430: 2		
HFLNA59	537447	88	101 - 319	1348	Pro-23 to Ala-30.	H0357: 2		
HFLQA82	757380	89	1 - 138	1349		H0357: 2		
HFLQF55	719018	90	3 - 230	1350		H0357: 1, L0157: 1, H0510: 1, L0438: 1, L0748: 1 and L0439: 1.		
HFLSF55	955305	91	221 - 385	1351	Pro-1 to Asn-6.	H0197: 3, H0199: 1 and H0246: 1.		
HFLSH67	968639	92	55 - 192	1352	Asp-31 to Gly-41.	H0197: 6, H0199: 2 and L0748: 1.		
HFLSI23	509743	93	282 - 416	1353	Pro-6 to Asp-11.	H0197: 2 and L0748: 1.		
HFLSJ61	507017	94	91 - 318	1354		H0197: 2 and H0199: 1.		
HFLSK11	964908	95	3 - 335	1355	Pro-5 to Ala-12.	H0197: 1, H0199: 1 and H0198: 1.		
HFLSK31	535238	96	207 - 329	1356	Lys-1 to Gly-8,	H0197: 1 and		



HFLSK81	761133	97	74 - 268	1357	Thr-23 to Val-32. Lys-13 to Asn-22.	H0246: 1. H0199: 2 and H0197: 1.		
HFLUF43	928026	98	176 - 316	1358	Lys-38 to Arg-47.	H0199: 3, H0047: 1 and H0246: 1.		
HFLUF44	522416	99	73 - 396	1359	Gly-19 to Glu-26, Pro-52 to Ser-58, Glu-84 to Gly-94.	H0199: 2	12	
HFLUG50	526181	100	105 - 200	1360		H0199: 2		
HFLVE61	539872	101	1 - 393	1361	Thr-17 to Gly-27.	L0581: 9, L0748: 6, H0574: 5, H0246: 5, H0632: 4, H0393: 3, H0199: 3, H0510: 2, S0438: 2, L0809: 2, L0615: 1, H0357: 1, H0643: 1, H0331: 1, L0021: 1, H0197: 1, H0355: 1, H0509: 1, L0806: 1, L0807: 1, L0665: 1, H0144: 1, H0520: 1, L0749: 1, L0750: 1 and L0757: 1.	3p21.2- p21.1	150250, 164500, 168468, 182280, 238310, 600163, 601226, 601916
HFLVE85	531014	102	224 - 376	1362	Pro-9 to Arg-23.	H0246: 2		
HFLVI15	921860	103	196 - 441	1363		H0197: 2 and H0246: 2.		
HFLVI52	954506	104	1 - 108	1364	Arg-18 to Arg-25.	H0197: 3 and		

HFVBA62	754154	105	55 - 330	1365			H0246: 3.		
HFVGI78	935839	106	1 - 174	1366			H0152: 1 and H0509: 1.		
HFVGK74	789130	107	53 - 277	1367			H0393: 2		
HFVHC25	678573	108	85 - 222	1368		Lys-26 to Gly-36.	H0393: 2		
HFVHE45	572837	109	198 - 380	1369		Thr-1 to Lys-6.	H0393: 2 and L0754: 1.		
HFVHE66	572852	110	98 - 319	1370			H0393: 2		
HFVHF81	929124	111	136 - 291	1371			H0393: 2		
HFVHI01	916970	112	214 - 354	1372		Gly-12 to Arg-20, Lys-35 to Phe-40.	H0393: 2		
HFVHM86	572830	113	2 - 289	1373			H0393: 2		
HFVHT75	573301	114	3 - 122	1374			H0393: 1 and H0014: 1.		
HFVIH95	573198	115	121 - 270	1375			H0393: 1 and H0036: 1.		
HFVII33	871980	116	2 - 271	1376			H0393: 2		
HGBAE29	537309	117	78 - 194	1377			H0014: 3		
HGBAH38	503211	118	10 - 108	1378			H0014: 2		
HGBAH80	932630	119	2 - 211	1379			H0014: 2		
HGBAI39	503055	120	189 - 326	1380			H0014: 2		
HGBAI42	503057	121	267 - 458	1381		Gly-1 to Glu-11.	H0014: 3		
HGBAI44	536599	122	75 - 278	1382		Lys-8 to Pro-29, Phe-46 to Asn-51.	H0014: 3		
HGBAI70	707918	123	106 - 216	1383		Gln-1 to Arg-7.	H0014: 2		
HGBAK23	500801	124	3 - 167	1384		Tyr-3 to Gln-27, Pro-29 to Arg-41.	H0014: 2		

HGBAM36	509552	125	10 - 180	1385	Tyr-11 to Leu-25.	H0014: 3		
HGBAM75	509546	126	79 - 198	1386		H0014: 2		
HGBAN21	509538	127	59 - 313	1387	Lys-5 to Trp-17.	H0014: 2		
HGBAO08	854321	128	88 - 210	1388		H0014: 3 and L0750: 1.	6q14	136550, 203310, 269920, 602772
HGBAP09	509265	129	9 - 266	1389	Ile-13 to Cys-19, Pro-21 to His-30, Leu-40 to Trp-48, Gly-60 to Ser-66.	H0014: 2		
HGBAP42	509262	130	13 - 165	1390		H0014: 3		
HGBAQ37	500799	131	135 - 230	1391		H0014: 3		
HGBAQ81	509533	132	100 - 216	1392		H0014: 2	17p11.2	100710, 182290, 201475, 270200, 601097, 601097, 601097, 602666
HGBAU10	961242	133	163 - 285	1393		S0444: 1, H0014: 1 and L0764: 1.		
HGBAU93	625250	134	1 - 252	1394	Asn-8 to Arg-13, Ser-33 to Ser-41, Asp-49 to Arg-56.	H0014: 1 and H0506: 1.		
HGBAZ13	971646	135	181 - 357	1395	Arg-1 to Cys-6.	H0014: 2		
HGBBB48	503470	136	161 - 301	1396	Leu-12 to Thr-18.	H0015: 2		

HGBBO62	509691	137	249 - 515	1397	Pro-14 to Ser-21.	L0748: 2, H0036: 1 and H0015: 1.		
HGBBY74	509641	138	31 - 201	1398	Pro-48 to Thr-53.	H0015: 2		
HGBCH13	508982	139	1 - 279	1399	Gln-51 to Gly-56.	H0015: 2		
HGBCU23	508807	140	168 - 281	1400	Glu-23 to Gln-28.	H0014: 1 and H0015: 1.		
HGBDB04	961510	141	2 - 280	1401	His-20 to Thr-33.	H0014: 2		
HGBDB21	753848	142	247 - 369	1402		H0014: 3		
HGBDC48	960971	143	160 - 366	1403	Ser-16 to Ser-22.	H0014: 5		
HGBDD52	954496	144	320 - 499	1404		H0014: 3, L0659: 1 and L0748: 1.	107280, 107280, 107400, 107400, 122500, 186960, 245200, 601841	
HGBDE16	533741	145	3 - 302	1405		H0014: 2		
HGBDF61	742234	146	171 - 455	1406	Lys-1 to Trp-6, Ala-8 to Asn-13, Ser-19 to Phe-24.	L0439: 2, S0354: 1, H0014: 1 and L0455: 1.		
HGBDG59	522932	147	1 - 372	1407	Ile-81 to Gln-88.	H0014: 2		
HGBDG69	578390	148	1 - 333	1408		H0014: 2		
HGBDH63	732530	149	157 - 62	1409	Glu-16 to Gly-24.	H0014: 2		
HGBDI95	509439	150	106 - 261	1410		H0014: 2		
HGBDL05	932881	151	343 - 537	1411	Pro-27 to Thr-32.	H0014: 1, H0509: 1, L0748: 1 and L0758: 1.		

HGBDL72	710318	152	75 - 374	1412	Ala-2 to Ala-7.	H0014: 3		
HGBDU57	731004	153	2 - 121	1413		H0014: 2		
HGBDX24	678576	154	178 - 321	1414		L0774: 2, L0756: 2, L0731: 2, H0014: 1, L0794: 1, L0803: 1, L0743: 1, L0777: 1 and S0446: 1.		
HGBDX35	503477	155	210 - 365	1415		H0014: 2		
HGBDY02	921081	156	61 - 225	1416		H0014: 2		
HGBDY30	503476	157	127 - 237	1417	Cys-7 to Leu-22.	H0014: 2		
HGBDY59	815818	158	3 - 455	1418	Pro-6 to Thr-11:	AR050: 68, AR054: 62, AR051: 50, AR089: 11, AR061: 7 H0622: 2, L0659: 2 and H0014: 1.		
HGBEY32	971570	159	114 - 227	1419		H0014: 2		
HGBGA29	508433	160	1 - 141	1420		H0014: 2		
HGBGI54	573764	161	107 - 271	1421		H0014: 2		
HGBGI57	573752	162	107 - 187	1422		H0014: 2 and L0803: 1.		
HGBGO22	558830	163	69 - 359	1423	Cys-1 to Cys-12, Thr-30 to Ser-55, Gly-59 to Val-66, Gly-70 to Val-75.	AR061: 7, AR089: 6 H0014: 2, L0790: 2, H0393: 1, H0036: 1, H0622: 1, L0662: 1, L0768:	188450, 188450, 188450	

								1, L0783: 1, L0809: 1, S0374: 1 and L0779: 1.			
HGBGT92	924780	164	2 - 166	1424	Arg-10 to Ala-15, Asp-27 to Arg-41.			H0014: 2			
HGBGW04	573644	165	14 - 187	1425	Gly-1 to Arg-8, Arg-14 to Trp-25, Ile-28 to Ala-41, Gly-43 to Gly-51.			H0014: 2			
HGBHC35	573687	166	3 - 314	1426	Gln-1 to Asn-6, His-12 to Gly-17.			H0014: 2			
HGBHM09	573673	167	7 - 186	1427	Glu-1 to Ala-9, Thr-36 to Arg-45, Pro-55 to Pro-60.			H0014: 2			
HGBHN46	573678	168	2 - 100	1428	Gly-15 to Gly-21, Leu-23 to Ser-31.			H0014: 3			
HGBHP95	781326	169	3 - 197	1429	His-1 to Ala-8.			H0014: 2			
HGBHS11	967385	170	79 - 225	1430	Tyr-26 to Glu-34.			H0014: 2			
HGBHY06	937940	171	3 - 296	1431	His-1 to Phe-7.			H0263: 1 and H0014: 1.			
HGBIC81	796500	172	1 - 108	1432	Asn-1 to Trp-7.			H0014: 2			
HGBID55	575197	173	118 - 249	1433	Asn-1 to Ser-8.			H0014: 1 and H0015: 1.			
HGOCB25	506771	174	171 - 347	1434				H0018: 2			
	668759	1260	178 - 59	2520	Ile-3 to Lys-9, Pro-34 to Gln-40.						
HHLBA18	527530	175	51 - 164	1435				T0091: 2			
HISAC25	678054	176	83 - 307	1436	Lys-58 to Gly-69.			L0598: 1, H0539:			

									1, S0378: 1, L0748: 1 and L0698: 1.			
HISAI35	707172	177	1 - 123	1437	Ala-6 to Asn-15.				H0539: 2			
HISAM61	974576	178	299 - 541	1438	Arg-29 to Lys-35.				H0539: 3			
HISAN16	661752	179	183 - 374	1439	Ala-3 to Leu-10, Gln-22 to Gly-27, Ser-29 to Cys-36.				H0539: 2			
HISAN47	710943	180	190 - 47	1440	Ser-12 to Trp-20, Pro-28 to Ser-41.				H0539: 2, L0022: 1, L0649: 1 and L0592: 1.	18p11.22-p11.21		
HISAT61	488809	181	197 - 373	1441	Lys-3 to Asp-11.				H0539: 2			
HISBA01	916165	182	141 - 260	1442					H0539: 2			
HISBB09	964344	183	13 - 129	1443					H0539: 2 and L0753: 1.			
HISBB67	751467	184	9 - 269	1444					H0539: 2			
HISBE32	677148	185	275 - 424	1445	Val-17 to Ser-37.				H0539: 3			
HISBG13	657005	186	45 - 170	1446	Trp-16 to Asn-22, Ile-37 to Thr-42.				H0539: 2 and L0748: 1.			
HISBH10	964359	187	40 - 318	1447	Ser-20 to Leu-36, Arg-48 to Gln-61.				H0539: 2			
HISBJ96	796306	188	1 - 318	1448	Pro-6 to Arg-26, Pro-35 to Gly-51.				H0539: 2			
HISBO64	745884	189	28 - 135	1449					H0539: 2			
HISBT02	919509	190	137 - 295	1450	Gly-43 to Gln-48.				H0539: 3			
HISBU45	717604	191	3 - 434	1451	Glu-42 to Asn-67, Gly-93 to His-100, Ser-121 to Gly-126.				H0539: 3, L0657: 1 and L0777: 1.			
HISBU68	693115	192	19 - 174	1452	Arg-14 to Arg-19.				H0539: 2			

HISBW20	669525	193	155 - 412	1453		H0539: 2, L0746: 1 and L0758: 1.		
HISCF72	740183	194	34 - 252	1454	Gln-17 to Arg-27.	H0539: 2		
HISCH85	761973	195	1 - 276	1455	Ser-4 to Gly-14, His-33 to Gly-47, Gly-63 to Ala-73.	S0374: 1 and H0539: 1.		
HISCH83	831507	196	105 - 374	1456	Ser-1 to Asp-16.	H0539: 2 and L0747: 1.		
HISCK85	857497	197	16 - 258	1457		H0539: 2		
HISCL06	935079	198	48 - 245	1458	Gly-50 to Trp-59.	H0539: 2		
HISCN24	764837	199	148 - 300	1459	Lys-9 to Asn-14.	H0539: 2		
HISCP11	966171	200	2 - 376	1460	Pro-7 to Pro-12.	H0539: 2		
HISCV30	883892	201	248 - 532	1461		H0014: 1, H0539: 1, L0748: 1 and L0756: 1.		
HISDM43	974583	202	265 - 585	1462	His-1 to Glu-6, Glu-15 to Asp-20, Thr-48 to Ser-53, Asp-61 to Trp-69.	H0574: 1, H0539: 1 and L0779: 1.		
HISDO59	857479	203	498 - 776	1463		H0085: 1 and H0539: 1.		
HISDS91	787603	204	31 - 189	1464		H0539: 2 and L0747: 1.		
HISDT82	790966	205	170 - 490	1465		H0539: 2		
HISDU39	745914	206	358 - 534	1466		H0539: 2		
HISDV63	788753	207	193 - 375	1467		H0539: 2		
HISDZ80	775474	208	46 - 420	1468	Pro-5 to Arg-17, Arg-24 to Pro-29.	H0539: 2		



HISEA07	952295	209	1 - 102	1469	Leu-9 to Pro-19.	H0539: 2 and L0439: 1.		
HISEE71	759828	210	3 - 170	1470	Lys-24 to Ser-32.	H0539: 2		
HISEJ18	783919	211	2 - 142	1471		H0539: 2		
HISEJ39	789809	212	188 - 334	1472	Ser-11 to Arg-19.	H0539: 2		
HISEN88	760209	213	121 - 318	1473		H0539: 2		
HISES80	775598	214	126 - 275	1474		H0539: 2		
HLDAK38	689904	215	91 - 225	1475	Gln-5 to Leu-11.	H0509: 3		
HLDBF84	924101	216	444 - 809	1476	Leu-49 to Gln-55.	L0748: 24, H0574: 5, L0581: 4, H0510: 3, H0509: 3, H0331: 2, H0632: 2, L0749: 2, H0057: 1, H0014: 1 and L0794: 1.		
HLDBJ86	882365	217	30 - 452	1477		H0509: 2, H0510: 1 and L0774: 1.		
HLDBR32	752494	218	173 - 310	1478	Lys-2 to Asn-11.	H0509: 1 and H0539: 1.		
HLDC51	871341	219	14 - 169	1479		H0509: 1 and H0595: 1.		
HLDCG82	657567	220	381 - 542	1480	Pro-36 to Asp-41.	H0509: 1 and H0539: 1.		
HLDCI35	831356	221	66 - 725	1481	Val-39 to Lys-47, Cys-81 to Trp-86.	AR061: 3, AR089: 1 L0748: 7, L0791: 2, H0597: 1, H0509: 1, L0803: 1,		

								L0804: 1 and L0581: 1.			
HLDLCU27	950724	222	2 - 316	1482	Asp-16 to Gly-30, Pro-34 to Gly-48, Val-50 to Lys-55, Ser-61 to Asp-70, Pro-73 to Gly-78.			AR061: 2, AR089: 1 H0509: 2, L0774: 2, H0393: 1, H0184: 1, L0471: 1, L0363: 1, L0768: 1, L0375: 1, L0634: 1, L0809: 1, L0743: 1 and L0777: 1.			
HLDH01	926360	223	3 - 326	1483	Ala-14 to Arg-21, Pro-67 to Arg-72.			AR089: 2, AR061: 2 H0509: 1 and H0478: 1.			
HLDI91	790003	224	258 - 608	1484	Glu-1 to Ser-18; Lys-62 to Ile-67.			AR089: 0, AR061: 0 H0355: 1, H0509: 1 and L0748: 1.			
HLDK12	923442	225	108 - 242	1485	Asn-19 to Pro-33, Lys-40 to Asp-45.			H0590: 1 and H0509: 1.			
HLDL55	875000	226	456 - 262	1486	Thr-19 to Ser-29.			H0509: 2, L0774: 2, H0393: 1, H0184: 1, L0471: 1, L0363: 1, L0768: 1, L0375: 1, L0634: 1, L0809: 1, L0743: 1 and L0777: 1.			
HLDNJ57	733903	227	1 - 261	1487				L0748: 2, L0758: 8p22			148370,

								2, H0574: 1, H0510: 1, S0438: 1 and L0665: 1.		238600, 238600, 238600, 238600, 600143, 601385, 602629
HLDNU53	883158	228	2 - 478	1488	Leu-10 to Glu-28, Ala-32 to Ala-54, Ser-62 to Ser-69, Gly-78 to Arg-92.			L0748: 14, L0803: 5, L0749: 5, H0331: 2, H0510: 2, L0766: 2, L0581: 2, H0574: 1, H0632: 1, L0774: 1, L0439: 1, L0750: 1 and L0777: 1.		
HLDOA63	949166	229	69 - 521	1489	Leu-2 to Gln-9, Pro-11 to Gln-26, Lys-65 to Pro-70.			AR089: 17, AR061: 16 H0510: 2, L0581: 2 and H0355: 1.		
HLDOB53	728220	230	76 - 189	1490				H0510: 2		
HLDOG86	682265	231	83 - 163	1491				H0574: 2, H0510: 2, L0749: 2, H0331: 1, L0021: 1 and L0748: 1.		
HLDON90	788891	232	2 - 145	1492	Lys-1 to Arg-10.			AR089: 7, AR061: 3 H0622: 2, L0535: 2, H0510: 1, H0039: 1, L0369: 1, L0748: 1 and		

HLDOR73	683262	233	132 - 269	1493	Phe-7 to Asn-31.	L0749: 1.		
HLDOU12	857106	234	167 - 370	1494	Thr-20 to Gly-26, Leu-49 to Ser-55.	H0510: 2 H0510: 4, H0509: 1 and S0380: 1.		
HLDOZ69	697988	235	1 - 351	1495	Asn-23 to Ser-31, Thr-74 to Thr-82.	H0510: 2		
HLDP A63	744341	236	114 - 257	1496	Arg-19 to Phe-27.	H0510: 2		
HLDQA88	796173	237	1 - 246	1497		H0510: 1 and H0595: 1.		
HLDQB65	708002	238	1 - 168	1498	Arg-1 to Trp-7, Gly-12 to Gly-23, Ile-27 to Lys-32, Arg-47 to Val-56.	H0510: 3 and L0731: 1.		
HLDQC62	923559	239	838 - 1083	1499	Arg-40 to Leu-45.	L0748: 5, H0510: 4, H0632: 1, H0509: 1 and L0749: 1.		
HLDQH10	932015	240	130 - 318	1500		H0510: 2 and L0755: 1.		
HLDQQ76	953312	241	37 - 321	1501	Glu-22 to Ser-28, Arg-59 to Pro-67.	H0510: 3, L0581: 2, L0662: 1 and L0777: 1.		
HLDRD44	697576	242	451 - 645	1502	Phe-7 to Tyr-13, Thr-32 to Lys-39.	L0803: 10, H0510: 6, H0355: 4, L0581: 3, H0393: 2, L0775: 2, H0574: 1, H0632: 1, H0098: 1, H0014: 1, H0509: 1, L0804: 1,		

									L0790: 1, H0144: 1 and L0748: 1.			
HLDRE54	727954	243	83 - 265	1503		Val-4 to Asn-10, Pro-44 to Arg-50.			H0510: 2			
HLDRE26	681284	244	17 - 187	1504		Lys-5 to Asn-14.			H0574: 2, H0510: 2 and L0754: 1.			
HLDRE66	966517	245	60 - 206	1505		His-12 to Gln-17, Leu-39 to Thr-44.			H0510: 2			
HLDRI94	784582	246	10 - 114	1506		Trp-4 to Gln-11.			L0748: 2, H0098: 16 1 and H0510: 1.			
HLDRI14	657908	247	3 - 188	1507					S0376: 1, H0510: 1 and L0752: 1.			
HLDRO82	837031	248	3 - 461	1508		Arg-13 to Glu-20, Asn-26 to Asp-32, Thr-57 to Asn-82.			L0581: 3 and H0510: 2.			
HLDRI54	708594	249	1 - 180	1509		Thr-5 to Arg-11, Gln-21 to Ile-44.			H0510: 2			
HLIBI35	870387	250	1 - 195	1510		Pro-10 to Ala-17.			H0574: 1 and H0355: 1.			
HLIBJ13	910830	251	3 - 422	1511		Thr-1 to Gly-23, Asn-33 to Gly-40, Arg-45 to Gln-50, Arg-70 to Phe-77.			AR061: 3, AR089: 2 L0803: 10, H0510: 6, H0355: 5, L0581: 3, H0393: 2, L0775: 2, H0574: 1, H0632: 1, H0098: 1, H0014: 1, H0509: 1, L0804: 1, L0790: 1, H0144: 1			

HLIBO03	923519	252	206 - 316	1512			and L0748: 1.			
HLIBP66	750608	253	91 - 171	1513			H0355: 2			
HLIBZ48	721023	254	8 - 235	1514		Ser-8 to Thr-18.	H0355: 2			
HLICR73	837030	255	1 - 444	1515		Asp-41 to Gly-47, Pro-65 to Thr-72, Thr-90 to Phe-95.	H0015: 1, H0355: 1 and L0749: 1.			
HLICT47	929754	256	116 - 355	1516		Thr-20 to Arg-26, Leu-30 to Ser-35.	AR061: 9, AR089: 2 H0510: 3, L0393: 1, H0355: 1 and L0581: 1.			
HLICT57	734451	257	1 - 186	1517		Ser-19 to Ala-25, Glu-31 to Thr-41, Ser-49 to Arg-54.	H0355: 2			
HLIPBD66	928708	258	24 - 218	1518		His-1 to Arg-19.	H0349: 3			
HLQAF70	529348	259	94 - 174	1519		Gly-20 to Asn-27.	H0331: 2			
HLQAL33	702755	260	54 - 344	1520			L0754: 2, H0331: 1 and H0622: 1.			
HLQAN64	966910	261	439 - 113	1521			L0748: 3, L0749: 2, H0331: 1, H0574: 1, L0774: 1 and H0506: 1.	3p21.3-p22	116806, 120120, 120120, 120120, 120120, 120436, 120436, 120436, 138320, 168468, 182280,	

									190182, 190182, 227646, 261510, 600163, 601154
HLQAZ69	960046	262	2 - 199	1522	Ala-1 to Gln-12, Ala-15 to Arg-23.	H0331: 2			
HLQBF72	608371	263	108 - 284	1523	Ser-1 to Phe-7.	AR089: 25, AR061: 9 H0331: 2			
HLQBH46	527923	264	49 - 213	1524	Asp-13 to Asn-20.	H0331: 2			
HLQBI21	529342	265	204 - 464	1525		H0574: 3, H0331: 20p12 2, H0510: 2, H0632: 1, L0021: 1, L0803: 1 and L0748: 1.		112261, 176640, 176640, 176640, 236700, 601920	
HLQBL71	542262	266	79 - 162	1526		H0331: 2			
HLQBX13	856783	267	2 - 163	1527		AR054: 16, AR050: 11, AR051: 2 H0331: 2			
HLQBX23	676205	268	184 - 330	1528		H0331: 2			
HLQCN58	706239	269	131 - 244	1529	Arg-22 to Arg-27.	H0574: 2, H0331: 1 and L0697: 1.			
HLQCY26	681459	270	176 - 271	1530		H0574: 2			
HLQDB55	731601	271	233 - 361	1531		H0574: 2			

HLQDC82	779697	272	1 - 147	1532		S0358: 2, L0666: 2, L0748: 2, L0751: 2, H0574: 1, L0770: 1, L0764: 1, L0771: 1, L0806: 1, L0519: 1, L0438: 1, L0745: 1, L0747: 1, L0749: 1, L0777: 1, L0731: 1, L0608: 1 and L0593: 1.		
HLQDE61	741706	273	102 - 266	1533	Gln-9 to Thr-17, Gln-30 to Lys-36, Ser-42 to Val-48.	H0331: 1 and H0574: 1.		
HLQDP11	966775	274	47 - 328	1534		H0574: 2		
HLQDU40	488692	275	3 - 185	1535	His-3 to Tyr-9, His-39 to Cys-44.	L0766: 5, H0574: 2 and L0365: 1.		
HLQDY10	856755	276	153 - 416	1536	Tyr-13 to Lys-18, Lys-38 to Gln-43, Gly-66 to Trp-72.	H0574: 2		
HLQED11	966015	277	20 - 202	1537	Pro-15 to Pro-21, Pro-27 to Glu-32.	H0574: 1 and H0632: 1.		
HLQEH54	871683	278	292 - 531	1538	Ser-13 to Phe-19, Gln-47 to Glu-75.	L0748: 9, L0749: 5, L0777: 2, H0574: 1 and H0349: 1.		
HLQES58	856725	279	11 - 226	1539	Asn-31 to Leu-37.	H0331: 1 and H0574: 1.		
HLQEY16	856712	280	157 - 375	1540	Phe-21 to Gln-28.	H0574: 1 and S0374: 1.		
HLQFD23	856701	281	317 - 448	1541		H0574: 2		



HLQFO69	933385	282	245 - 553	1542	Asn-1 to Glu-7.	AR089: 1, AR061: 1 S0360: 1 and H0574: 1.		
HLQKG74	856736	283	475 - 864	1543	Glu-28 to His-39, Arg-49 to Lys-56.	L0748: 14, L0803: 5, L0749: 5, H0331: 2, H0510: 2, L0766: 2, L0581: 2, H0574: 1, H0632: 1, L0774: 1, L0439: 1, L0750: 1 and L0777: 1.		
HLQGN56	842004	284	201 - 431	1544	Arg-45 to Gly-51.	L0748: 3, H0331: 1, H0632: 1 and H0509: 1.		
HLXTF06	931101	285	72 - 293	1545	Pro-19 to Arg-25, Gln-32 to Lys-37, Pro-48 to Arg-54.	S0450: 2		
HNAAA40	574045	286	173 - 328	1546		H0379: 2		
HNAAE33	574001	287	11 - 190	1547		H0379: 2		
HNAAE73	922929	288	67 - 348	1548	Pro-1 to Gly-11, Pro-18 to Pro-24.	H0379: 1 and H0380: 1.	22q13.31	250100, 250800, 250800
HNALD49	723168	289	373 - 609	1549	Cys-43 to Gly-56.	H0380: 2 and L0747: 1.		
HNJBA08	955993	290	380 - 1453	1550	Lys-1 to Met-11, Glu-21 to Asp-28, Arg-44 to Ala-51, Glu-98 to His-106, Thr-173 to Ile-179,	H0632: 1 and S0328: 1.		

						Asn-209 to Ala-219, Thr-256 to Thr-261, Arg-267 to Lys-280, Asp-299 to Lys-305, Glu-329 to Lys-334.					
HNJBB04	927458	291	22 - 171	1551		Lys-11 to Arg-16.				S0328: 2	
HNJBJ80	947047	292	311 - 490	1552		Asp-1 to Gly-12.				H0622: 1, L0646: 1, L0790: 1, S0328: 1 and L0596: 1.	
HNJBL71	939266	293	71 - 616	1553		Asp-1 to Asn-7, Arg-17 to Leu-23, Leu-32 to Gln-46, Pro-63 to Pro-70, Ala-87 to Gln-92, Ser-165 to Leu-170.				S0328: 1 and S0330: 1.	2
HNJBN94	948996	294	1 - 639	1554		Leu-40 to Asn-45.				AR089: 1, AR061: 1 S0328: 13, S0330: 7, S0464: 1 and S0350: 1.	
HNJBW16	955920	295	254 - 481	1555		Pro-1 to Leu-7, Val-11 to Arg-18.				S0328: 4	
HNJCD23	961494	296	89 - 292	1556		Arg-1 to Gly-37, Arg-39 to Asn-53, Val-61 to Lys-68.				S0328: 3	
HNJCH53	969065	297	434 - 745	1557		Lys-52 to Ala-57.				S0328: 4, L0662: 2, L0666: 2, L0731: 2, L0803: 1 and L0665: 1.	

HNJEA92	955842	298	46 - 837	1558	Arg-175 to Arg-180, Cys-188 to Gly-193.	S0330: 183, S0328: 86, H0593: 16, S0456: 3, S0446: 3, H0619: 2, H0042: 1, H0575: 1, L0508: 1, S0350: 1 and L0600: 1.		
HNJEC12	969099	299	461 - 661	1559		L0744: 5, S0328: 3, L0731: 3, L0805: 2, L0806: 1 and L0666: 1.		
HNJFC68	956178	300	358 - 495	1560	Pro-38 to Lys-46.	S0328: 3, L0766: 2 and L0779: 1.		
HNKBB44	955843	301	834 - 274	1561	Arg-98 to Arg-103, Cys-111 to Gly-116.	S0330: 24, S0328: 3, L0789: 1 and H0593: 1.		
HNKBR49	955844	302	65 - 274	1562	Lys-13 to Asn-24, Lys-40 to Gln-49, Asp-58 to Ala-70.	S0330: 183, S0328: 86, H0593: 16, S0456: 3, S0446: 3, H0619: 2, H0042: 1, H0575: 1, L0508: 1, S0350: 1 and L0600: 1.		
HNKBS78	955565	303	799 - 227	1563		S0330: 16, S0328: 2, L0806: 1 and L0600: 1.		
HNKBV10	961542	304	209 - 451	1564		S0330: 3		
HNKCF21	951659	305	1 - 993	1565	Asn-25 to Tyr-44, Ala-80 to Asn-86,	S0330: 9 and S0328: 6.		

							Ala-105 to Asp-119, Pro-161 to Cys-170, Ser-174 to Phe-180, Glu-182 to Trp-187, Phe-190 to Gln-195, Lys-221 to Ala-233, Tyr-261 to Met-267, Thr-310 to Ser-331.				
HNKCG51	933428	306	342 - 689	1566			Ser-64 to Leu-71, Thr-74 to Ser-79, Phe-95 to Asp-106.		L0766: 4, S0330: 2, L0777: 2, L0748: 1, L0751: 1 and L0731: 1.		
HNKDV89	963354	307	282 - 440	1567			Arg-9 to Ser-15, Tyr-18 to Gly-24.		L0756: 3, L0768: 2, L0794: 2, L0005: 1, L0520: 1, L0766: 1, L0803: 1, S0374: 1, L0438: 1, S0330: 1, L0779: 1 and L0759: 1.		
HOCNE77	832202	308	2 - 217	1568			Thr-7 to Gly-17.		S0442: 1 and S0374: 1.		
HPASB03	925360	309	1 - 291	1569					H0270: 1 and S0378: 1.		
HPASD70	522675	310	121 - 234	1570					L0774: 3; L0803: 2, S0374: 2, S0354: 1, S0358: 1, H0270: 1, H0036: 1 and L0758: 1.		
HPKAA65	753931	311	27 - 146	1571			Ser-32 to His-40.		H0478: 170.		

HROAF59	961784	312	2 - 259	1572		S0392: 80, H0479: 33, H0447: 29, H0448: 17, H0096: 15, H0486: 10, S0330: 6, H0485: 3, H0510: 2, H0035: 2, S0280: 1, H0038: 1, H0488: 1, S0352: 1, H0509: 1, H0522: 1, S0432: 1 and H0542: 1.	S0376: 1 and H0316: 1.	5q31	121050, 131400, 138040, 153455, 159000, 179095, 181460, 192974, 192974, 600807, 601596, 601692, 601692, 601692, 602089, 602121, 602460
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HROAL51	526487	313	73 - 213	1573			H0316: 2		
HROAO26	531173	314	1 - 129	1574			H0316: 2		
HROAT53	669179	315	169 - 273	1575			H0316: 2		
HROAV94	963714	316	70 - 294	1576		Ser-1 to Asn-14.	H0316: 1 and H0598: 1.		
HROBC76	880935	317	3 - 248	1577			AR061: 9, AR089: 3 H0598: 2		
HROBF58	735601	318	45 - 362	1578		Arg-34 to Lys-40.	H0598: 2		
HROBF77	677615	319	67 - 225	1579			H0316: 1 and H0598: 1.		
HROBM06	934681	320	52 - 210	1580		Pro-48 to Pro-53.	H0316: 1 and H0598: 1.		
HROBQ03	867044	321	169 - 399	1581		Lys-6 to Lys-12.	H0598: 2		
HROBV96	867038	322	265 - 459	1582			H0598: 2		
HROBX40	835594	323	3 - 209	1583		Pro-27 to Asn-35.	H0316: 1 and H0598: 1.		
HROCE61	741263	324	93 - 212	1584			H0316: 1 and H0598: 1.		
HRODC11	966298	325	28 - 183	1585			H0598: 2		
HRODF69	766014	326	103 - 342	1586		Pro-16 to Lys-23, Pro-44 to Pro-50.	H0598: 2		
HRODH54	922899	327	2 - 142	1587			S0354: 2 and H0598: 1.		
HRODJ28	685922	328	423 - 599	1588			H0598: 2		
HRODP45	717316	329	1 - 267	1589		Pro-20 to Asn-32, Pro-34 to Asp-43.	H0316: 1 and H0598: 1.		
HRODV70	841930	330	128 - 280	1590		Ser-11 to Ser-17.	H0316: 2 and		

									H0598: 1.			
HRODX50	722502	331	26 - 127	1591					H0598: 2			
HROEA83	710615	332	31 - 255	1592			Lys-17 to Cys-31, Thr-47 to Gln-57.		H0598: 2 and L0517: 1.			
HROEB10	963706	333	100 - 213	1593					H0598: 1 and H0343: 1.			
HSGSC41	576407	334	33 - 179	1594			Lys-26 to Gly-38.		H0447: 3, H0448: 3 and L0772: 1.			
HSIAL23	508122	335	58 - 165	1595					H0331: 1 and H0036: 1.			
HSICN48	524767	336	103 - 294	1596			Val-15 to Ala-23, Lys-34 to Glu-42.		H0036: 2			
HSICO48	529162	337	2 - 82	1597					H0036: 1 and H0343: 1.			
HSICP51	531307	338	102 - 254	1598			Pro-3 to Trp-16.		H0036: 2	21q22.3	120220, 120240, 123580, 151385, 171860, 190685, 236100, 236200, 240300, 267750, 600065, 601072, 601145	
HSICR32	507173	339	187 - 80	1599					H0036: 2			
HSICR69	531061	340	127 - 273	1600			Ser-14 to Lys-19.		AR089: 2, AR061:			

								1				
HSICU08	960072	341	128 - 238	1601		Pro-15 to Gly-20, Pro-22 to His-37.		H0036: 2				
HSICV54	575344	342	2 - 157	1602				H0036: 2				
HSICV78	712629	343	175 - 369	1603		Gly-41 to Gly-54.		H0036: 2	17q25		114290, 138033, 162100, 170500, 170500, 170500, 180860, 264470	
HSICX21	531267	344	223 - 378	1604		Asn-5 to His-12.		AR089: 2, AR061: 0				
HSICY35	713308	345	53 - 238	1605		Glu-10 to Ser-25.		H0036: 2				
HSIDA42	531264	346	102 - 212	1606		Gln-10 to Ser-15, Met-23 to Ser-29.		H0590: 2 and H0036: 1.				
HSIDD83	531260	347	102 - 389	1607		Glu-17 to Gly-30, Glu-34 to Gly-40, Lys-60 to Pro-65, His-84 to Arg-90.		H0036: 2				
HSIDG40	531071	348	92 - 310	1608		Pro-11 to Cys-17, Pro-31 to Pro-39.		H0036: 2				
HSIDH73	531293	349	150 - 314	1609		His-3 to Pro-9.		H0036: 2				
HSIDJ20	526993	350	2 - 256	1610				H0036: 3 and L0759: 1.				



HSIDK12	531255	351	2 - 262	1611			H0036: 2		
HSIDO23	526974	352	62 - 190	1612	Lys-1 to Pro-14, Pro-25 to Glu-39.		H0036: 3 and L0471: 1.		
HSIDP49	531064	353	28 - 168	1613			H0036: 2		
HSIDS36	531251	354	241 - 396	1614			H0036: 2		
HSIDT29	522341	355	177 - 329	1615			H0036: 3		
HSIDT51	874598	356	17 - 331	1616	Thr-8 to Val-20, Pro-43 to His-48, Gln-52 to Gln-58.		H0036: 2		
HSIDV27	531246	357	137 - 319	1617	Val-10 to Leu-22.		H0036: 2		
HSIDV70	925083	358	43 - 186	1618			H0036: 2		
HSIDV75	531265	359	110 - 280	1619	Pro-12 to Lys-17, Phe-45 to Ser-52.		H0036: 2		
HSIDV82	531297	360	40 - 240	1620	Tyr-1 to Val-6.		H0036: 2	10q25.2- q26.3	263700
HSIDW39	775139	361	1 - 501	1621			AR051: 12, AR054: 9, AR061: 5, AR089: 2, AR050: 0 H0036: 2, H0590: 2, S0354: 1, H0510: 1 and L0748: 1.		
	830774	1261	12 - 419	2521	Glu-40 to Trp-57, Tyr-59 to Phe-64, Glu-91 to Arg-99, Asp-106 to Arg-114.				
HSIDX79	712026	362	165 - 299	1622			H0036: 2 and H0590: 1.		

HSIDZ20	920867	363	2 - 109	1623	Pro-18 to Glu-23.	H0036: 2		
HSIEE78	904664	364	1 - 1044	1624	Thr-5 to Ser-12, Pro-26 to Ser-31, Gln-46 to Gly-52.	AR054: 10, AR050: 9, AR051: 2 S0358: 5, S0354: 4, L0596: 3, S0356: 2, H0036: 2, H0590: 2, L0771: 2, L0758: 2, S0376: 1, S0360: 1, T0109: 1, L0040: 1, H0039: 1, H0038: 1, H0616: 1, L0646: 1, L0764: 1, L0768: 1, L0775: 1, L0659: 1, S0374: 1, S0404: 1 and H0506: 1.		
						H0036: 2		
						H0036: 2		
						H0036: 1 and H0590: 1.		
						H0036: 2		
						H0590: 2		
						H0590: 2		
						H0590: 1 and H0039: 1.		
						H0590: 2, H0036: 1 and L0601: 1.		
HSIEH45	531294	365	151 - 300	1625				
HSIEH84	531300	366	1 - 153	1626				
HSIEO17	922867	367	1 - 1017	1627				
HSIEO62	531249	368	16 - 222	1628				
HSIFa06	866573	369	62 - 334	1629				
HSIFa29	690277	370	180 - 338	1630				
HSIFC65	733694	371	1 - 333	1631	Leu-16 to Arg-31, Leu-39 to Gly-61, Ser-68 to Leu-79.			
HSIFE08	839907	372	325 - 690	1632				

HSIFE23	675419	373	229 - 435	1633			H0590: 2		
HSIFE28	686056	374	160 - 14	1634	Met-26 to Trp-31.		H0590: 2		
HSIFE46	718731	375	40 - 231	1635			H0036: 2 and H0590: 1.	2p23	143450, 182601, 264600, 278300, 600890, 600890, 601071, 602134
HSIFH48	721310	376	101 - 448	1636	Ser-1 to Ser-8, Pro-22 to Cys-30.		L0803: 4, H0590: 3, L0774: 3, S0380: 3, L0748: 2, L0771: 1, L0809: 1, L0789: 1, L0743: 1 and L0779: 1.		
HSIFN66	742966	377	2 - 211	1637	Asp-6 to Asp-18.		H0590: 2		
HSIFP22	674018	378	2 - 223	1638	Ala-12 to Gly-25, Pro-51 to Glu-62.		H0036: 2 and H0590: 2.		
HSIFR56	733024	379	151 - 330	1639	Pro-8 to Pro-13.		H0590: 2		
HSIFS23	919109	380	3 - 299	1640	Pro-15 to Glu-20, Trp-78 to Gly-88.		H0590: 3		
HSIFV95	836996	381	155 - 496	1641	Gly-5 to Asp-11, Gln-26 to Arg-32.		H0590: 1, L0591: 1 and H0506: 1.		
HSIFW89	771820	382	194 - 307	1642			H0590: 2		
HSIFW94	765203	383	70 - 309	1643	Arg-13 to Ser-19.		H0590: 2		
HSIFX92	968352	384	83 - 193	1644			L0534: 1, H0036: 1 and H0590: 1.		

HSIFZ21	670415	385	72 - 263	1645	Arg-7 to Ser-17.	H0590: 2, L0109: 1 and H0622: 1.		
HSIFZ51	919096	386	51 - 230	1646	His-12 to Trp-17, Val-25 to Glu-36.	H0590: 3		
HSIGA08	866568	387	1 - 282	1647	Trp-1 to Gly-22, Pro-24 to Pro-30, Ser-43 to Ser-51.	H0590: 2		
HSIGA28	686047	388	11 - 274	1648	Thr-1 to Pro-12, Leu-26 to Gln-31, Ser-41 to His-46.	H0590: 2 and L0562: 1.		
HSIGA33	701963	389	1 - 186	1649	Cys-8 to Arg-17.	H0590: 2		
HSIGD07	952508	390	220 - 324	1650	Arg-15 to Ile-21.	H0590: 1 and H0598: 1.		
HSIGD94	961040	391	72 - 200	1651		H0036: 1 and H0590: 1.		
HSIGF11	866552	392	3 - 143	1652		H0590: 3		
HSIGG58	735682	393	1 - 279	1653		H0590: 2		
HSIGG95	795631	394	130 - 291	1654		H0590: 2		
HSIGH52	726384	395	1 - 234	1655	Arg-13 to Gly-18.	H0590: 2		
HSIGJ45	718728	396	3 - 167	1656	Ser-1 to Glu-8, Glu-21 to Glu-26.	H0590: 2		
HSIGL56	906942	397	390 - 88	1657	Lys-10 to Asn-15, Thr-17 to Glu-22, Lys-38 to Gln-49, Leu-54 to Gly-59, Ala-62 to Ser-70, His-95 to Pro-101.	H0036: 1, H0590: 1 and L0599: 1.		
HSIGL94	769754	398	53 - 166	1658	Gly-25 to Pro-33.	H0590: 2		

HSIGM43	716259	399	72 - 278	1659	Arg-37 to Gln-42.	H0590: 2	
HSIGM67	751278	400	2 - 163	1660	Gln-1 to Gln-7, Trp-21 to Lys-28.	H0590: 2	
HSIGO07	893712	401	185 - 57	1661		H0590: 2	
HSIGO67	751262	402	1 - 408	1662	Arg-11 to Pro-16.	H0590: 2	
HSOAT94	537505	403	72 - 152	1663		H0343: 2	
HSOAW33	702709	404	117 - 278	1664		H0343: 1 and H0595: 1.	
HSOAW39	866228	405	26 - 139	1665		H0343: 2	
HSOBF59	738861	406	63 - 218	1666	Met-1 to Ser-12, Tyr-20 to Phe-26.	H0595: 2	
HSOBF65	747484	407	87 - 269	1667		H0595: 2	
HSOBL03	923317	408	100 - 288	1668	Lys-34 to Trp-44.	H0595: 2	
HSOBL58	735589	409	187 - 321	1669		H0595: 2	
HSOBL59	738858	410	2 - 130	1670	Arg-1 to Gly-7, Lys-32 to Cys-41.	H0595: 2	
HSOBP77	771729	411	1 - 189	1671		H0595: 2	
HSOBQ06	934666	412	269 - 379	1672	Thr-30 to Lys-37.	H0595: 2	
HSOBQ14	719796	413	3 - 134	1673		H0595: 2	
HSOBQ82	779093	414	109 - 288	1674		H0595: 2	
HSOBZ60	739915	415	115 - 210	1675	Lys-27 to Lys-32.	H0595: 2	
HSODB93	785711	416	288 - 416	1676	Pro-23 to Cys-29, Glu-35 to Ile-41.	H0343: 1 and H0595: 1.	
HSODO56	835876	417	64 - 159	1677	Tyr-1 to Arg-7, Gln-24 to Lys-29.	H0590: 1 and H0595: 1.	
HSODT01	915544	418	41 - 277	1678		H0595: 2	
HSODZ10	963671	419	24 - 368	1679	Asn-12 to Leu-18, Lys-52 to Lys-59.	H0595: 2	

							Leu-69 to Pro-74, Pro-85 to Lys-107.			
HSODZ58	731545	420	3 - 311	1680			Thr-95 to Phe-101.		H0539: 1, L0749: 1 and H0595: 1.	
HSOEC07	952397	421	66 - 200	1681			Ser-11 to His-16.		H0343: 1 and H0595: 1.	
HSPAF44	761986	422	184 - 387.	1682			Val-58 to Tyr-64.		H0478: 3	
HSPAK46	968901	423	9 - 440	1683			Pro-1 to Gly-11, Arg-43 to Arg-57, Ser-64 to Gly-69, Arg-74 to Thr-79.		H0478: 2	
HSPAL44	754600	424	100 - 225	1684					H0478: 2 and L0758: 1.	
HSPAM95	918857	425	1 - 120	1685					H0478: 2	
HSPAP89	775813	426	280 - 558	1686					H0478: 1 and H0595: 1.	
HSPAQ91	789887	427	136 - 429	1687					H0539: 1 and H0478: 1.	
HSPBG79	771630	428	52 - 399	1688			Gln-12 to Lys-18.		H0478: 2	
HSPBL63	727687	429	435 - 674	1689			Ser-16 to Gly-27.		H0478: 3 and S0392: 1.	
HSPBM18	786056	430	185 - 334	1690					H0478: 3 and S0392: 1.	
HSPME73	915722	431	46 - 798	1691			Pro-21 to Ile-28, Ile-32 to Phe-39, Pro-71 to Leu-82.		AR089: 3, AR061: 2 S0370: 1, H0479: 1 and L0439: 1.	
HSPMG03	920267	432	290 - 508	1692			Lys-1 to Glu-11.		H0478: 2 and	

HTNTD72	870030	433	3 - 302	1693	Met-24 to Ala-29, Pro-60 to Glu-66. Leu-14 to Trp-29.	H0479: 1.		
HTPAA30	509812	434	7 - 99	1694		H0039: 2		
HTPAC06	960791	435	1 - 159	1695		H0039: 2		
HTPAF01	961063	436	228 - 347	1696		H0039: 2		
HTPAG78	773936	437	228 - 386	1697		H0039: 2		
HTPBH46	522888	438	179 - 313	1698		H0039: 2		
HTPBQ47	922777	439	184 - 444	1699		H0622: 2 and H0039: 1.		
HTPBT55	509264	440	75 - 221	1700	Ser-19 to Gln-35.	H0039: 2		
HTPCD84	783263	441	13 - 90	1701	Glu-1 to Ser-7, His-13 to Ala-19, Gly-21 to Arg-26.	H0039: 2		
HTPCCK55	732458	442	30 - 104	1702		H0039: 2		
HTPCN85	529760	443	3 - 221	1703		H0039: 2		
HTPCO32	973306	444	209 - 316	1704	Arg-7 to Arg-14.	H0039: 3		
HTPCR51	526406	445	115 - 228	1705		H0039: 2		
HTPCS70	529766	446	3 - 323	1706	Asn-7 to Gly-12, Ser-29 to Ser-37.	H0039: 2, H0622: 2 and S0380: 1.		
HTPCT55	592481	447	1 - 342	1707	Gly-1 to Pro-19, Ala-45 to Thr-61.	H0039: 2		
HTPCT67	573704	448	113 - 346	1708	Gln-16 to His-25, Pro-27 to Ser-32.	H0039: 2, L0754: 1 and L0780: 1.		
HTPCT82	869886	449	3 - 248	1709	Thr-44 to Gln-49.	H0039: 2		
HTPCV62	573698	450	1 - 297	1710	Lys-1 to Met-10, Met-28 to Gly-38.	H0039: 2		

								Lys-57 to Arg-65, Pro-73 to Gly-88.				
HTPCV73	573686	451	199 - 384	1711					H0039: 2			
HTPCW69	935946	452	176 - 373	1712					H0039: 3			
HTPCZ07	953769	453	3 - 143	1713				Ile-10 to Arg-18, Asn-22 to Ser-27, Ile-35 to Asn-40.	H0039: 2			
HTPDI16	830553	454	3 - 197	1714					H0039: 2			
HTPDJ03	924789	455	193 - 426	1715				Gly-12 to Arg-18, Asn-20 to Trp-26, Pro-68 to Ser-78.	H0039: 2			
HTPDJ94	669158	456	10 - 258	1716				Ser-4 to Leu-13, Ala-15 to Phe-28, Val-53 to His-59, Gln-72 to Lys-82.	H0039: 2	9q34	125270, 125270, 128100, 137350, 191100, 215700, 223360, 268900, 601850	
HTPDK32	699457	457	57 - 257	1717					L0790: 2, H0039: 1, L0598: 1, L0639: 1, L0438: 1 and S0330: 1.			
HTPDS34	526416	458	222 - 404	1718					H0039: 2			
HTPDS85	541837	459	2 - 124	1719				Gln-27 to Lys-41.	H0039: 2			
HTPDT70	573727	460	2 - 118	1720				Gln-1 to Phe-8.	H0039: 2			
HTPDU59	973279	461	89 - 283	1721				Asn-10 to Glu-29,	H0039: 3			



HTPDV73	912947	462	276 - 752	1722	Ser-34 to Gln-49. Asp-14 to Ile-20.	AR089: 0, AR061: 0 H0039: 2			
HTPDW56	573706	463	1 - 99	1723	Gly-1 to Arg-6, Arg-13 to Ser-33.	H0039: 2			
HTPDW62	965356	464	170 - 337	1724	Ser-40 to Ser-47.	H0039: 2, S0358: 1 and L0764: 1.			
HTPDZ94	660751	465	155 - 343	1725		H0039: 2			
HTPEH20	573667	466	231 - 392	1726	Glu-5 to Phe-14.	H0039: 2 and L0758: 1.			
HTPFA05	869865	467	53 - 271	1727		H0622: 2			
HTPFD02	974295	468	61 - 354	1728		H0622: 5			
HTPFI35	874323	469	3 - 404	1729	Glu-7 to Tyr-12, Phe-14 to Asn-19, Glu-22 to Ser-28, Glu-36 to Ser-43, Ser-68 to Arg-73.	S0356: 2, H0622: 2 and L0766: 1.			
HTPFJ95	933120	470	271 - 402	1730	Asp-23 to Arg-28.	H0622: 2 and H0039: 1.			
HTPFM01	914956	471	99 - 284	1731	Gln-1 to Ile-7.	H0622: 2			
HTPFM04	926728	472	146 - 433	1732	Ile-35 to Tyr-42, Val-50 to Ala-55.	H0039: 1 and H0622: 1.			
HTPFN90	926462	473	3 - 218	1733		H0622: 2			
HTPFQ07	869785	474	3 - 212	1734	Pro-32 to Pro-41, Pro-59 to Gly-70.	H0622: 8	6p21	180297, 248611, 251000, 263200,	

										600211, 600701, 601690
HTPFS01	914908	475	2 - 325	1735		Cys-2 to Thr-16, Pro-63 to Gly-68, Pro-89 to Gly-102...	H0039: 1 and H0622: 1.			
HTPFW04	926537	476	94 - 252	1736		Ser-12 to Pro-17.	H0622: 2			
HTPFX77	961059	477	7 - 138	1737		Lys-16 to Thr-21, Phe-25 to Phe-34.	H0622: 3 and H0039: 1.			
HTPFY31	869839	478	19 - 150	1738			H0622: 2, L0623: 1, L0803: 1, L0527: 1 and L0759: 1.			
HTPFY43	869844	479	183 - 368	1739			H0622: 2 and L0751: 1.			
HTPFY73	906905	480	293 - 502	1740		Glu-23 to Ile-32.	H0039: 2, H0622: 2 and L0369: 1.			
HTPFZ03	922755	481	168 - 425	1741		His-1 to Asp-6, Arg-28 to Arg-33.	H0622: 3 and H0039: 1.			
HTPGD19	869842	482	160 - 555	1742		Pro-14 to Ser-20, His-35 to Leu-40.	H0622: 3			
HTPGE28	974302	483	318 - 635	1743		Lys-13 to Asn-18.	H0622: 4 and H0039: 1.			
HTPGF79	974301	484	323 - 442	1744			H0622: 2 and H0539: 1.			
HTPGG12	969538	485	245 - 541	1745			H0622: 4 and H0039: 1.			
HTPGK10	963169	486	1 - 189	1746		Gly-1 to Val-7, Thr-9 to Pro-15,	H0622: 2			

						Leu-27 to Tyr-32, Pro-44 to Lys-57.				
HTPGL49	974015	487	84 - 359	1747		Ala-48 to Ala-64.	1747		H0622: 4	
HTPGR61	869802	488	99 - 317	1748		Lys-1 to Pro-7, Pro-14 to Lys-25.	1748		H0622: 2, L0750: 1 and S0434: 1.	
HTPGW12	969522	489	1 - 192	1749		Asp-1 to Gln-13, Gln-39 to Glu-44, Asp-52 to Val-64.	1749		AR061: 8, AR089: 3 H0039: 1 and H0622: 1.	
HTPHD53	869795	490	47 - 400	1750		Gln-10 to Phe-18, Pro-58 to Gly-67.	1750		H0622: 3	
HTPHE36	869814	491	385 - 600	1751		Gly-6 to Asn-11.	1751		H0622: 2	
HTPHG90	914955	492	1 - 120	1752		Arg-13 to Ala-18, Pro-33 to Glu-39.	1752		H0622: 3	
HTPHI08	958077	493	2 - 355	1753		Asn-6 to Glu-13, Tyr-23 to Trp-30, Ser-38 to Cys-43.	1753		H0039: 2 and H0622: 1.	
HTPHK06	975310	494	242 - 42	1754		Gly-24 to Val-29.	1754		H0622: 3	
HTPHR76	869791	495	3 - 227	1755			1755		L0777: 2, H0622: 1, S0374: 1 and L0749: 1.	
HTPHS37	960637	496	3 - 338	1756			1756		H0039: 1 and H0622: 1.	
HTPHT28	952088	497	77 - 259	1757			1757		H0622: 2 and L0665: 1.	
HTPHV17	926455	498	38 - 172	1758			1758		H0622: 2	
HTPIC25	975319	499	1 - 462	1759		Pro-59 to Lys-64.	1759		H0622: 4	
HTPIE48	911422	500	2 - 313	1760		Pro-23 to Gly-33,	1760		H0622: 3 and 19p13.3	108725,

					Arg-42 to Gly-50, Asn-54 to Glu-59.	H0039: 1.		120700, 133171, 136836, 145981, 147141, 164953, 188070, 600957, 601238, 601846, 602216, 602477
HUFAA81	777951	501	224 - 442	1761	Asp-1 to Glu-8.	H0506: 2		
HUFAC65	750264	502	3 - 203	1762	Ile-52 to His-63.	H0506: 2		
HUFAG81	966223	503	2 - 178	1763	Ser-1 to Gly-11, Arg-16 to Cys-22, Pro-29 to Arg-34.	S0356: 1 and H0506: 1.		
HUFAJ29	690591	504	3 - 185	1764	Pro-4 to Gly-13.	H0506: 2		
HUFAL90	788868	505	3 - 128	1765	Pro-34 to Pro-42.	H0506: 2		
HUFAN64	678677	506	39 - 221	1766	His-1 to Phe-11, Pro-33 to Gly-39.	H0331: 1 and H0506: 1.		
HUFAP02	919805	507	355 - 468	1767	Ile-1 to Thr-15.	H0506: 2		
HUFAU25	678024	508	1 - 309	1768	Gln-5 to Gly-15.	AR089: 2, AR061: 1 L0794: 5, S0450: 1, L0662: 1, L0768: 1, L0790: 1, L0748: 1, L0439: 1, L0596: 1 and H0506: 1.		

HUFBA27	966256	509	1 - 219	1769			H0595: 1 and H0506: 1.		
HUFBN27	868997	510	42 - 401	1770	Thr-9 to Asn-15, Arg-44 to Phe-50.		H0598: 1 and H0506: 1.		
HUFBU14	868993	511	116 - 469	1771	Gly-1 to Ser-7, Gln-12 to Asp-19.		H0506: 2		
HUFBU41	712256	512	276 - 464	1772	Glu-10 to Leu-16, Thr-18 to Asp-27.		H0506: 2		
HUFBU61	741770	513	10 - 180	1773	Thr-11 to Asn-20, Pro-47 to Asn-52.		H0506: 2		
HUFBV27	683030	514	8 - 286	1774			H0506: 2		
HUFDB55	950430	515	2169 - 553	1775			AR050:10, AR054: 8, AR051: 2, AR089: 2, AR061: 0, S0358: 2, L0769: 2, L0646: 2, L0764: 2, S0404: 2, S0406: 2, S0408: 1, H0085: 1, H0204: 1, H0597: 1, L0794: 1, L0776: 1, L0518: 1, L0789: 1 and L0596: 1.		
HUFGH78	659722	516	2 - 340	1776	Gln-19 to Arg-24.		S0360: 2, H0590: 2, S0358: 1, H0510: 1, H0509: 1 and H0506: 1.		
HUVDJ10	886207	517	573 - 953	1777	Asn-18 to Gln-26, Arg-95 to Glu-107.		S0358: 45, S0354: 22, H0590: 8,		

							S0374: 7, H0036: 5, S0404: 4, H0623: 3, H0170: 2, S0356: 2, S0444: 2, H0085: 2, H0231: 2, H0056: 2, L0764: 2, H0171: 1, S0376: 1, S0408: 1, H0263: 1, L0040: 1, H0232: 1, H0597: 1, H0494: 1, L0627: 1, L0765: 1, L0777: 1, L0731: 1 and H0506: 1.		
	961825	1262	526 - 326	2522					
HVAEE01	915732	518	138 - 314	1778			L0439: 2, H0675: 1, L0763: 1, L0772: 1, L0606: 1, L0666: 1, L0438: 1, S0378: 1, L0748: 1, L0745: 1, L0750: 1 and L0594: 1.		
HVAEE94	968675	519	95 - 244	1779	Ser-27 to Pro-32.		S0378: 2		
HVACL61	868572	520	243 - 524	1780	Arg-4 to Ala-9, Gln-12 to Asn-18.		H0510: 2, S0378: 1, L0740: 1 and L0777: 1.		
HVAEM04	940469	521	19 - 93	1781			S0358: 1 and S0378: 1.		
HVAET61	965365	522	438 - 698	1782	Ile-1 to Asn-8.		AR089: 74, AR061: 66		

								S0378: 3, L0776: 2, L0805: 1, L0809: 1 and L0789: 1.		
HVAFD06	933527	523	300 - 629	1783	Asp-6 to Ala-12, Asn-14 to Pro-19.			S0378: 2		
HVAHA06	933531	524	25 - 249	1784				S0378: 2 and L0581: 1.		
HVAME35	968676	525	621 - 965	1785	Thr-14 to Gln-22, Ala-52 to Gly-70, Cys-94 to Thr-103.			S0378: 6 and S0380: 3.		
HVAMW07	951733	526	1 - 405	1786	Pro-4 to Arg-16.			S0380: 2		
HVAND08	958443	527	2 - 376	1787	Arg-10 to Ser-23.			S0408: 1 and S0380: 1.		
HVANR45	930308	528	151 - 606	1788	Arg-45 to Asp-50, Pro-111 to Gly-118.			S0380: 66, S0378: 64, S0368: 6, L0758: 3, L0778: 2, T0023: 1, L0794: 1 and L0790: 1.		
HVAOG11	966135	529	226 - 861	1789	Asn-16 to Ser-23, Lys-53 to Asp-60.			AR089: 2, AR061: 1, H0014: 1, H0039: 1, S0380: 1 and L0740: 1.		
HVAOK04	925932	530	50 - 178	1790	Gln-1 to Ser-6, Ser-16 to Gln-25, Ser-35 to Lys-43.			S0380: 3 and L0779: 1.		
HVAOW86	965298	531	69 - 440	1791	Ser-21 to Tyr-26.			L0740: 5, S0328: 2, L0748: 2, L0646: 1, L0387: 1, L0803: 1, L0804: 1, L0774: 1.		

								1, L0809: 1, S0380: 1, L0754: 1 and L0752: 1.			
HVARE86	965243	532	379 - 501	1792			Val-4 to Val-13, Pro-21 to Gly-40.	S0380: 4, L0757: 2, S0360: 1, L0021: 1, L0803: 1 and L0663: 1.			
HWCAG91	773364	533	71 - 247	1793				S0294: 3, L0766: 2 and H0085: 1.			
HWGAC19	668126	534	311 - 421	1794				S0370: 2			
HWGAC45	754792	535	3 - 206	1795				S0370: 2	8		
HWGAE55	974955	536	2 - 286	1796			Ser-4 to Asp-15, Ser-28 to Gly-33, Trp-36 to Trp-46.	S0370: 4 and S0374: 1.			
HWGQD52	726390	537	1 - 111	1797				S0382: 2			
HWGQF79	882611	538	1 - 366	1798			Lys-3 to Gly-11.	AR089: 40, AR061: 16, S0372: 1 and S0382: 1.			
HWLAL74	761974	539	26 - 166	1799			Arg-34 to Thr-40.	S0374: 2			
HWLBI74	839518	540	210 - 380	1800			Pro-35 to Gly-43.	S0374: 2			
HWLBJ06	934614	541	16 - 180	1801				S0360: 1, S0374: 1 and L0777: 1.			
HWLBK76	731099	542	8 - 163	1802				S0374: 2 and L0604: 1.			
HWLBK80	933865	543	116 - 547	1803			Glu-11 to Gly-16, Gln-28 to Phe-44, Pro-59 to Asp-68,	AR089: 7, AR061: 2, S0374: 2			



HWLCV54	929742	544	98 - 247	1804	Arg-73 to Gly-80, Arg-1 to Asn-12, Asn-41 to Tyr-47.	S0374: 2 and H0316: 1.			
HWLDO22	838721	545	41 - 205	1805	Arg-40 to Thr-46.	L0774: 3, L0803: 2, S0374: 2, S0354: 1, S0358: 1, H0270: 1, H0036: 1 and L0758: 1.			
HWLED58	830330	546	169 - 444	1806	Ser-1 to Arg-11, Ser-22 to Ala-33.	S0354: 3			
HWLEF86	785193	547	152 - 3	1807		S0354: 2			
HWLEH06	934649	548	187 - 555	1808	Glu-1 to Leu-6, Lys-37 to Gly-49, Arg-80 to Gly-87, Arg-92 to Ala-97.	S0354: 2			
HWLEH47	709376	549	1 - 258	1809		H0590: 3, S0354: 1 and H0506: 1.			
HWLEI16	729050	550	163 - 318	1810	Ser-15 to Asp-25.	S0354: 2			
HWLEJ07	952396	551	49 - 252	1811	Val-49 to Leu-56.	S0354: 2			
HWLEK39	918545	552	3 - 371	1812	Arg-35 to Glu-40, Pro-44 to Arg-52.	S0354: 2			
HWLEN08	958509	553	2 - 808	1813	Arg-1 to Asp-6, Glu-35 to Cys-59, Glu-62 to Leu-69, Arg-72 to Lys-89, Leu-97 to Phe-104, Val-108 to Lys-135, Gln-141 to Lys-149, Ile-156 to Ser-163.	S0354: 2			

								Lys-173 to Gly-206, Gly-235 to Gly-247.			
HWLEN20	963418	554	105 - 311	1814				Gly-6 to Gly-11, Glu-17 to Leu-24, Pro-44 to Thr-49.	S0354: 6		
HWLEO59	974078	555	3 - 212	1815				Lys-1 to Gly-7, Ala-21 to Ser-26, Arg-61 to Ala-66.	S0354: 11		
HWLEP95	751199	556	161 - 445	1816				Ala-17 to Val-34, Arg-36 to Pro-45.	S0354: 2		
HWLEQ36	966250	557	68 - 256	1817				Leu-1 to Ser-11, Asp-29 to Thr-35, Ser-44 to Ser-56.	S0354: 2		
HWLEQ81	934224	558	70 - 222	1818				Glu-1 to Lys-15, Gln-17 to Ser-22.	S0354: 2		
HWLER88	915168	559	21 - 143	1819				Lys-11 to His-23.	S0354: 2		
HWLFB08	849136	560	2 - 520	1820				Glu-10 to Leu-24, Lys-42 to Ala-48, Thr-105 to Ser-114.	S0354: 2		
HWLFC80	830279	561	180 - 311	1821				Gly-34 to Arg-44.	S0354: 2 and S0358: 1.		
HWLFE50	830283	562	419 - 592	1822					S0354: 3, L0515: 1 and L0779: 1.		
HWLFF40	830287	563	1 - 102	1823				Asn-2 to Phe-7.	S0354: 3		
HWLFF62	915155	564	85 - 420	1824				Gln-22 to Pro-29, Pro-39 to Pro-44.	S0354: 2		
HWLFH47	719752	565	30 - 167	1825					S0354: 2		
HWLFJ51	853602	566	79 - 210	1826					S0354: 3		

HWLKF50	918539	567	150 - 302	1827			S0354: 2		
HWLFO70	756554	568	167 - 397	1828			S0354: 2		
HWLFO82	779461	569	253 - 429	1829		Arg-22 to Glu-29.	S0354: 2		
HWLFO92	791052	570	3 - 137	1830			S0354: 2		
HWLFP37	708985	571	125 - 436	1831		Lys-63 to Ser-69.	S0354: 2		
HWLFP46	882848	572	2 - 235	1832		Thr-21 to Lys-32, Val-68 to Gly-77.	S0354: 2		
HWLFAQ48	721154	573	77 - 211	1833			S0354: 2		
HWLFS01	915531	574	192 - 374	1834			S0354: 2		
HWLFS86	830246	575	393 - 557	1835			S0354: 4		
HWLFW61	922924	576	1 - 147	1836			S0354: 2		
HWLFW01	915527	577	105 - 515	1837		Thr-25 to Gln-30, Ser-37 to Ile-43.	S0354: 2		
HWLGL36	806724	578	295 - 429	1838			S0354: 2		
HWLGP10	883139	579	37 - 318	1839		Ser-40 to Pro-46, Lys-51 to Gly-56, Pro-89 to Arg-94.	S0354: 3		
HWLGP21	958259	580	2 - 88	1840			S0354: 2		
HWLGR72	958284	581	73 - 300	1841		Asn-25 to Ser-33.	S0442: 1 and S0354: 1.		
HWLGT12	966044	582	36 - 350	1842		Thr-51 to Asp-60, Pro-78 to Thr-89.	S0354: 3		
HWLGT54	952732	583	534 - 704	1843			S0354: 1 and H0509: 1.		
HWLGV83	871680	584	69 - 308	1844		Pro-40 to His-45.	S0354: 1, H0574: 1 and L0518: 1.		
HWLGX56	830329	585	125 - 394	1845		Thr-42 to Ala-48, Gln-54 to Leu-78.	S0354: 6		

HWLHC73	830319	586					Thr-82 to Asn-89.			
HWLHF49	926878	587	365 - 496	1846			Cys-9 to Arg-18.	S0354: 4		
HWLHO01	915158	588	2 - 301	1848			Val-2 to Phe-7, Pro-11 to Phe-28, Pro-31 to Gln-59, Glu-72 to Gln-80, Trp-88 to Ser-94.	S0354: 1 and H0539: 1.		
HWLHP05	931087	589	201 - 389	1849				S0354: 2		
HWLHR93	952387	590	1 - 381	1850			Thr-31 to Trp-36.	S0354: 2		
HWLHT06	934217	591	38 - 235	1851			Ile-3 to Leu-11, Leu-27 to Gly-37, Pro-50 to Val-66.	S0354: 2		
HWLHT92	830322	592	228 - 458	1852				S0354: 3		
HWLIC75	830321	593	1 - 57	1853			Arg-1 to Gly-8, Lys-14 to Lys-19.	S0358: 4		
HWLIF03	830233	594	3 - 167	1854				S0358: 8		
HWLIH21	917551	595	32 - 817	1855				S0358: 10, H0263: 1 and H0478: 1.		
HWLIL65	747440	596	133 - 282	1856			Leu-18 to Lys-30.	S0358: 2		
HWLIM37	712654	597	14 - 88	1857			Arg-1 to Cys-7, Arg-12 to Tyr-19.	S0358: 2, L0766: 2, L0757: 2, L0731: 1 and L0608: 1.		
HWLIO73	761965	598	1 - 72	1858				S0358: 2		
HWLIS13	933552	599	118 - 363	1859				S0358: 40, S0374: 21, L0803: 14, S0360: 10, S0404:	134580, 145001, 145260,	

						10, S0444: 7, L0664: 6, L0599: 6, S0354: 5, S0376: 5, L0666: 5, L0373: 4, L0662: 4, H0597: 3, L0805: 3, S0328: 3, S0330: 3, L0744: 3, L0040: 2, L0374: 2, L0774: 2, L0776: 2, L0743: 2, S0356: 1, S0442: 1, S0408: 1, H0637: 1, H0596: 1, H0231: 1, L0738: 1, H0046: 1, H0050: 1, H0674: 1, S0370: 1, S0440: 1, L0646: 1, L0653: 1, L0809: 1, H0648: 1, H0672: 1, S0406: 1, H0506: 1 and L0600: 1.			150292, 208250, 226450, 276901, 600105, 600332, 600759, 600995, 601652, 601744, 601975
HWLIS62	722358	600	148 - 444	1860	His-68 to Arg-74, Ser-79 to Pro-86:	S0358: 2	Xq12-q13.3	300011, 300011, 300011, 300127, 305450, 309605, 313700, 313700.	

										313700, 313700, 313700, 314580
HWLIW68	925892	601	235 - 378	1861					S0358: 2	
HWLJB04	926066	602	233 - 364	1862					S0358: 2, L0774: 1 and L0756: 1.	
HWLJC30	830232	603	2 - 538	1863				Pro-23 to Lys-39, Ser-44 to Leu-74, Lys-77 to Leu-83, Phe-101 to Asn-106, Pro-122 to Trp-130, Asn-151 to Asp-157, Ala-159 to Pro-168.	S0358: 3, L0764: 2, L0803: 2, S0354: 1, H0085: 1, L0646: 1, L0775: 1, L0789: 1 and L0666: 1.	
HWLJE89	928258	604	460 - 585	1864					S0358: 4	
HWLJG57	849123	605	240 - 404	1865				Ser-26 to Leu-31.	S0358: 3 and L0558: 1.	
HWLJL14	832205	606	41 - 319	1866				Pro-62 to Ser-67, Asn-76 to His-81.	S0358: 1 and H0231: 1.	
HWLJL46	830226	607	87 - 200	1867					S0358: 6	
HWLJN54	729051	608	107 - 406	1868					S0358: 7, L0748: 3 and H0574: 1.	
HWLJN66	830229	609	304 - 513	1869				Glu-26 to Ser-35.	S0358: 5	
HWLJP79	963698	610	263 - 445	1870				Asp-29 to His-36.	S0358: 3	4
HWLJR77	883207	611	154 - 660	1871				Arg-26 to Arg-41, Val-80 to Asp-86, Ser-102 to Trp-107, Gly-125 to Thr-130.	AR061: 6, AR089: 1 S0358: 26, S0374: 15, S0354: 7,	

								S0444: 6, L0794: 5, S0408: 4, H0085: 4, H0597: 3, S0442: 2, L0771: 2, S0404: 2, H0194: 1, H0231: 1, L0738: 1 and L0372: 1.			
HWLJX38	925868	612	3 - 86	1872				S0358: 7			
HWLJZ30	925870	613	2 - 400	1873			Ile-1 to Cys-9, Asp-13 to Ser-20, Gln-44 to Gly-49, His-116 to Val-121.	S0358: 4			
HWLKC87	956205	614	2 - 133	1874			Phe-32 to Arg-38.	AR089: 5, AR061: 3, S0358: 2			
HWLKF70	830237	615	103 - 327	1875				S0358: 3			
HWLKL17	928720	616	100 - 273	1876			Arg-10 to Asp-15.	S0358: 2			
HWLKR35	918557	617	3 - 521	1877			Gly-8 to Lys-15, Ser-20 to Gln-27, Ser-30 to Met-36, Pro-62 to Trp-75, Pro-82 to Gly-113, Thr-122 to Lys-135, Gln-161 to Gly-169.	S0358: 4			
HWLKV34	957615	618	361 - 489	1878			Thr-17 to Leu-25, Asp-38 to Lys-43.	S0358: 5			
HWLKV91	830214	619	242 - 430	1879				S0358: 4 and L0748: 1.			
HWLKW04	969141	620	77 - 424	1880			Ser-17 to Leu-30, Pro-72 to Lys-81,	AR089: 52, AR061: 26			

								Glu-86 to Ser-95, His-105 to Asn-116.	S0358: 6			
HWLKW09	951716	621	373 - 570	1881				Leu-4 to Ser-11, Ser-37 to Ser-42, Lys-45 to Ser-51.	S0358: 3			
HWLKW17	860227	622	76 - 186	1882					S0358: 7			
HWLLB11	954849	623	51 - 524	1883				Pro-1 to Glu-10, His-60 to Arg-76, Pro-79 to Arg-85, Ala-95 to Ile-101, Glu-124 to Glu-130, Lys-151 to Arg-158.	AR061: 2, AR089: 2, S0358: 2, L0657: 1 and L0601: 1.			
HWLLH02	918427	624	128 - 259	1884				Gln-9 to Arg-19, Cys-21 to Lys-28.	S0358: 2			
HWLLH25	933479	625	31 - 135	1885					S0358: 5			
HWLLS11	965899	626	106 - 318	1886					S0358: 2, L0766: 1 and L0776: 1.			
HWLLT02	918419	627	2 - 253	1887				Lys-7 to Pro-12, His-43 to Glu-49.	S0358: 2			
HWLLV41	830150	628	2 - 286	1888				Thr-3 to Val-11, Glu-53 to Ser-67.	S0358: 7 and L0803: 1.			
HWLLX12	969681	629	1 - 177	1889					S0358: 3			
HWLMA84	929421	630	3 - 137	1890					S0376: 2			
HWLNX76	887583	631	3 - 365	1891					S0376: 2	7p15-pl4	10776, 138079, 138079, 139191, 142959.	



									153880, 180104, 203740, 600994, 601472, 601649
HWLPC29	965058	632	6 - 329	1892	Ser-17 to Asn-26, Tyr-48 to Tyr-53.	S0354: 1, L0138: 1 and S0374: 1.			
HWLPG05	930991	633	174 - 272	1893		S0374: 3			
HWLRA85	965400	634	442 - 591	1894		S0360: 2	5q31-q33		109690, 109690, 121050, 131400, 138040, 153455, 154500, 159000, 179095, 180071, 181460, 192974, 192974, 222600, 222600, 222600, 234000, 272750, 600807, 601411,

								601596, 601692, 601692, 601692, 601692, 602089, 602121, 602460
HWLUB86	966462	635	20 - 160	1895	Tyr-9 to Ser-15.	S0360: 1 and S0328: 1.		
HWLVF04	926880	636	363 - 479	1896	Thr-4 to Asp-9, Cys-21 to Ile-28.	S0360: 2		
HWLVO06	933592	637	112 - 303	1897		S0360: 2, L0655: 1 and L0666: 1.		
HWLVS52	925738	638	25 - 357	1898		S0360: 3		
HWLXE16	975258	639	108 - 344	1899	Pro-19 to Phe-26, Pro-29 to Gly-34, Pro-50 to Ser-55, Gly-67 to Lys-73.	S0360: 2		
HWLXO01	913808	640	218 - 514	1900	Val-20 to Pro-28, Glu-45 to Gly-53.	S0360: 2		
HWLZB12	969262	641	55 - 270	1901	Thr-1 to Phe-11, Ala-28 to Pro-38.	S0360: 2 and L0774: 1.		
HWMDAD05	931076	642	3 - 149	1902	Lys-32 to Ala-43.	S0354: 2		
HWMEI07	830227	643	14 - 139	1903		S0358: 6		
HWMEI48	830256	644	264 - 157	1904	Lys-1 to Pro-15.	S0358: 19, S0114: 1 and H0436: 1.		
HWMEI65	969190	645	2 - 382	1905	Asp-30 to Trp-35,	AR089: 17,		

							Ser-38 to Arg-43.	AR061: 11, S0358: 2 and H0539: 1.		
HWMFUE56	922375	646	2 - 199	1906			Leu-12 to His-18.	S0358: 4		
HWMFA28	965354	647	3 - 173	1907			Ser-6 to Asn-16, Ser-33 to Pro-45.	S0358: 8		
HWMFGL10	963406	648	296 - 439	1908				S0358: 2		
HWMFGL32	883180	649	145 - 321	1909				S0358: 4		
HWMFGL23	849129	650	169 - 2	1910			Leu-21 to Ser-35.	S0358: 4		
HWMFQ90	928646	651	2 - 175	1911			Arg-45 to Trp-53.	S0358: 2		
HWMFY21	974325	652	104 - 298	1912			Pro-9 to Cys-23, Lys-31 to Ile-38.	S0358: 2		
HWMGL13	947969	653	1 - 423	1913			Ser-4 to Thr-10, Trp-26 to Gly-31, Pro-63 to Gly-71.	S0358: 2		
HWMHG06	933534	654	253 - 399	1914			Val-7 to Ser-13.	S0358: 2		
HWMHG26	957665	655	129 - 326	1915			Pro-9 to Pro-27, Arg-39 to Glu-44, Phe-61 to Leu-66.	S0358: 2 and L0758: 1.		
HWMHS10	961647	656	148 - 417	1916			Thr-22 to Ser-27, Glu-81 to Trp-87.	S0358: 2		
HWMHT22	917570	657	82 - 297	1917				S0358: 2		
HWMHX12	914007	658	3 - 737	1918				S0358: 9		
HWMHZ25	951699	659	110 - 355	1919			Glu-26 to Phe-34.	S0358: 3		
HWMID39	915686	660	198 - 467	1920			Cys-6 to Thr-11.	S0358: 2		
HWMIR03	922302	661	208 - 53	1921			Glu-3 to Pro-9, Leu-28 to His-34.	S0358: 2		
HWMJB68	914031	662	157 - 336	1922			Pro-55 to Leu-60.	S0358: 3		

HWMIJ50	933501	663	32 - 76	1923			S0358: 2		
HWMIK101	913841	664	2 - 226	1924	Ser-46 to Pro-67.		S0358: 2 and L0744: 1.		
HWMIK110	961616	665	1 - 354	1925	Arg-19 to Gly-26.		S0358: 3	4q31	107250, 181600, 189800, 266300
HWMLG23	961110	666	2 - 247	1926	Pro-3 to Val-18, Val-34 to Ser-39, Ala-73 to Ser-78.		S0358: 2		
HWMMAI2	969173	667	153 - 254	1927	Gln-1 to Asn-12, Lys-17 to Lys-30.		S0358: 2		
HWMMG65	928823	668	513 - 782	1928			S0358: 2, L0809: 2, L0803: 1 and L0783: 1.		
HWMMS65	917513	669	192 - 395	1929			S0358: 2		
HWMMY66	966367	670	21 - 155	1930	Gly-1 to Val-18.		S0358: 2		
HWMNC07	951724	671	2 - 49	1931	Asp-7 to Lys-16.		S0358: 3		
HWNAG05	928811	672	452 - 724	1932	Ala-1 to Asp-10, Ser-19 to Ser-25, Pro-45 to Asp-50.		L0005: 1, S0360: 1, H0036: 1, L0142: 1, L0143: 1, L0383: 1 and L0748: 1.		
HWNB06	933578	673	3 - 314	1933	Cys-2 to Gly-7.		S0356: 1 and S0360: 1.		
HWNB06	933587	674	186 - 374	1934	Asp-1 to Lys-8, Lys-44 to Thr-51.		S0360: 3		
HWNCY59	927487	675	237 - 73	1935	Ser-1 to Lys-6.		S0360: 2		
HWNEO76	929720	676	52 - 189	1936			S0360: 2		

HWNEX05	928784	677	57 - 185	1937			S0360: 2		
HWNEY06	933551	678	371 - 628	1938	His-24 to Thr-29.		S0360: 2, H0632: 1, L0740: 1, L0777: 1 and L0759: 1.		
HWNFZ48	933522	679	3 - 191	1939	Gln-6 to Gln-11, Lys-51 to Phe-63.		S0360: 2		
HWNGN09	961602	680	34 - 339	1940	Arg-19 to Val-28, Ile-41 to Phe-58.		AR089: 2, AR061: 1 S0360: 2		
HWNHA12	969205	681	625 - 422	1941	Thr-7 to Val-12, Ser-20 to Leu-26.		S0360: 3		
HXOAI14	974075	682	380 - 634	1942			S0466: 5 and S0464: 1.		
HXOAA67	974326	683	32 - 232	1943	Asn-22 to Pro-35.		S0466: 1		
HWNHN10	961609	684	3 - 659	1944	Thr-4 to Ser-10, Glu-12 to Asn-18, Pro-31 to Pro-43, Glu-79 to Glu-97, Gln-107 to Leu-112, Ser-136 to Trp-143, Pro-150 to Trp-172, Pro-183 to Cys-195, Thr-204 to Lys-212.		L0779: 2 and S0360: 1.		
HWNDU11	965382	685	40 - 303	1945	Gly-1 to Val-8, Pro-17 to Cys-23, Cys-38 to Thr-44, Arg-76 to Asn-85.		S0360: 1 and L0777: 1.		
HWNCN05	928791	686	113 - 811	1946	Gly-28 to Gly-34, Pro-39 to Phe-46,		L0750: 2, S0360: 1 and L0759: 1.		

HWNBX05	928800	687	298 - 414	1947	Pro-75 to Asp-90. Cys-22 to Ala-31.	S0360: 1 and L0439: 1.			
HWNBL12	969222	688	3 - 86	1948		S0360: 1, L0717: 1, L0777: 1 and L0755: 1.			
HWNAL06	933591	689	294 - 425	1949	Thr-12 to Gln-22, Thr-33 to Ser-41.	S0360: 1 and L0759: 1.			
HWNAE01	914082	690	492 - 782	1950	Glu-1 to Leu-12, Arg-83 to Gln-97.	L0748: 3, L0743: 2, L0749: 2 and S0360: 1.			
HWMGO10	961716	691	23 - 169	1951		S0358: 1, L0717: 1, L0770: 1, L0518: 1, L0666: 1, L0747: 1 and L0752: 1.	21q22.2	176261, 601399	
HWMBY62	937234	692	135 - 479	1952		S0376: 1 and L0749: 1.	18		
HWMBM89	968984	693	161 - 54	1953		L0747: 2, L0755: 2, S0376: 1, L0369: 1, L0775: 1, L0777: 1 and L0759: 1.			
HWMAE12	969692	694	3 - 515	1954	Gln-6 to His-16, Ser-39 to Met-45, Asn-57 to Arg-71, Glu-78 to Gln-83, Val-110 to Thr-117, Ser-130 to Val-147.	S0354: 1, L0529: 1 and L0741: 1.			
HWLXJ10	963328	695	44 - 283	1955	Arg-15 to Ser-26.	S0360: 1 and L0803: 1.			

HWLVU33	972979	696	2 - 340	1956	Ser-50 to Pro-56, Pro-68 to Val-77.	S0360: 1 and L0758: 1.		
HWLVK02	922696	697	412 - 212	1957	Ser-29 to Pro-34, Arg-47 to Thr-62.	L0755: 3, L0776: 2, S0360: 1, L0763: 1 and L0756: 1.		
HWLUY15	874966	698	156 - 308	1958		S0360: 1, L0776: 1 and L0758: 1.		
HWLQS70	933799	699	379 - 528	1959	Ala-5 to Met-10, Ser-44 to Arg-50.	L0766: 4, S0360: 1, L0771: 1 and L0731: 1.		
HWLQA64	918932	700	96 - 164	1960		S0360: 1 and L0439: 1.		
HWLPN12	969572	701	170 - 337	1961	Thr-25 to Thr-39.	L0766: 2, S0374: 1, L0759: 1 and L0485: 1.		
HWLOL02	918320	702	191 - 301	1962		S0376: 1, L0521: 1, L0750: 1 and L0779: 1.		
HWLOB68	908500	703	6 - 401	1963		AR061: 1, AR089: 1 S0376: 1 and L0740: 1.		
HWLNC88	875790	704	387 - 572	1964	Thr-12 to Phe-19, Lys-57 to Lys-62.	L0803: 2, S0376: 1, L0763: 1 and L0759: 1.		
HWLNA36	974863	705	607 - 317	1965		L0794: 3, L0803: 2, S0376: 1, L0774: 1, L0665: 1 and L0731: 1.		

HWLMI16	918726	706	236 - 400	1966		S0376: 1 and L0759: 1.		
HWLLZ91	887157	707	2 - 463	1967	Ser-35 to Ser-47.	AR051: 1, AR050: 1, AR054: 0 S0358: 1		
HWLLD02	930932	708	432 - 265	1968		S0358: 1 and L0662: 1.	10	
HWLKT19	974292	709	1 - 261	1969		S0358: 1		
HWLKQ11	965390	710	3 - 122	1970		S0358: 1		
HWLKI18	930414	711	207 - 473	1971		S0358: 1		
HWLKI03	922371	712	253 - 468	1972		S0358: 1 and L0776: 1.		
HWLJW12	969556	713	50 - 241	1973	Ser-32 to Trp-37, His-48 to Tyr-55.	S0358: 1 and L0764: 1.		
HWLJW11	924518	714	260 - 451	1974	Pro-23 to Ser-29.	S0358: 1 and L0747: 1.		
HWLJU91	789882	715	45 - 254	1975	Ser-24 to His-40.	S0358: 1, L0748: 1 and L0596: 1.		
HWLJP28	925655	716	22 - 204	1976		S0358: 1, L0766: 1 and L0750: 1.		
HWLJM40	710519	717	204 - 416	1977	Pro-33 to Lys-38, Lys-49 to Asn-57.	S0358: 1 and L0747: 1.		
HWLJK01	914089	718	334 - 504	1978	His-7 to Leu-12.	S0358: 1 and L0774: 1.		
HWLIS95	795416	719	109 - 231	1979		S0358: 1 and L0744: 1.		
HWLIG05	928226	720	101 - 217	1980		S0358: 1 and L0747: 1.		



HWLID27	682563	721	275 - 427	1981			S0358: 1 and L0754: 1.		
HWLHW01	915161	722	193 - 351	1982			S0354: 1, L0775: 1 and L0758: 1.		
HWLHU03	922931	723	218 - 406	1983			L0539: 1 and S0354: 1.		
HWLHK09	949288	724	276 - 707	1984	Ser-1 to Arg-12, Glu-19 to Arg-24, Gly-36 to Ser-41, Arg-73 to Pro-79.		S0354: 1 and L0775: 1.		
HWLHH62	876225	725	20 - 277	1985	Met-1 to Trp-10.		L0754: 2 and S0354: 1.		
HWLHD19	887203	726	3 - 632	1986			AR051: 11, AR050: 9, AR054: 8 S0354: 1		
HWLGV14	967914	727	46 - 444	1987			AR061: 42, AR089: 3 S0354: 1 and L0748: 1.		
HWLGA04	925682	728	174 - 344	1988			L0766: 3, S0354: 1 and L0751: 1.		
HWLFY91	789569	729	405 - 572	1989	His-8 to Met-14, Gly-16 to Lys-31.		S0354: 1 and L0605: 1.		
HWLFY06	934635	730	15 - 296	1990	Pro-12 to Gln-22, Thr-34 to Phe-42, Leu-53 to Thr-65, Leu-73 to Gly-80.		L0749: 3, S0354: 1, L0769: 1 and L0806: 1.		
HWLFV52	950978	731	70 - 357	1991	Pro-27 to Gly-34.		S0354: 1 and		

HWLFQ39	705200	732	3 - 236	1992			L0759: 1. L0438: 7, L0439: 5, L0805: 2, L0415: 1, S0354: 1, L0787: 1 and L0741: 1.		
HWLFM69	754644	733	2 - 559	1993			L0777: 2 and S0354: 1.		
HWLFH36	708387	734	2 - 142	1994		Arg-10 to Asp-15.	S0354: 1 and L0754: 1.		
HWLFB71	759915	735	279 - 596	1995		Gln-11 to Glu-18, Asn-57 to Glu-64.	S0354: 1 and L0748: 1.		
HWLEZ11	966228	736	372 - 539	1996		Lys-24 to Gly-46.	S0354: 1 and L0605: 1.		
HWLEQ61	741224	737	59 - 205	1997		Ser-18 to Trp-32.	L0439: 2 and S0354: 1.		
HWLEM80	886651	738	27 - 671	1998		Arg-11 to Val-19, Tyr-23 to Asp-48, Ser-61 to Gly-96.	AR051: 18, AR050: 1 S0354: 1		
HWLEM01	915547	739	144 - 314	1999			S0354: 1 and L0526: 1.		
HWLEL08	860161	740	328 - 576	2000		Gly-17 to Arg-23, Arg-55 to His-60.	AR050: 97, AR054: 84, AR051: 70 S0354: 1		
	908147	1263	334 - 582	2523		Gly-17 to Arg-23, Arg-55 to His-60.			
HWLEK75	766928	741	463 - 567	2001			S0354: 1, L0742: 1, L0748: 1 and		

HWLEI57	734267	742	389 - 195	2002	Thr-35 to Ala-43.	L0592: 1. AR050: 109, AR051: 105, AR054: 100 S0354: 1		
HWLEH70	874721	743	2 - 454	2003	Gly-11 to Ser-23, Lys-41 to Gln-48, Lys-70 to Asp-77.	S0354: 1 and L0749: 1.		
HWLEF27	682572	744	2 - 268	2004	Gln-6 to Pro-26, Pro-28 to Phe-44, Arg-54 to Ile-67, Leu-80 to Gly-89.	S0354: 1 and L0439: 1.		
HWLEA48	927676	745	100 - 408	2005	Pro-1 to Thr-8.	AR089: 1, AR061: 0 S0354: 1 and L0596: 1.		
HWLDX03	922806	746	2 - 187	2006	Gly-13 to Trp-21.	L0763: 1, S0374: 1 and L0747: 1.		
HWLDB04	887051	747	1 - 297	2007	Pro-6 to Ser-11.	AR051: 25, AR054: 20, AR050: 20, AR089: 1, AR061: 0 S0374: 1		
HWLCM06	934117	748	170 - 406	2008		L0533: 1 and S0374: 1.		
HWLCG42	975246	749	321 - 503	2009	Lys-11 to His-16, Ser-28 to Thr-36, Ala-46 to Gln-55.	L0641: 1 and S0374: 1.		

HWLCD10	974071	750	485 - 102	2010		S0374: 1		
HWLBO06	934630	751	22 - 243	2011	Pro-32 to Asp-61.	L0021: 1, L0803: 1, S0374: 1 and L0752: 1.		
HWLBN90	787355	752	392 - 610	2012	Gly-34 to Glu-41, Glu-46 to Arg-53, Thr-62 to Val-68.	S0374: 1 and L0777: 1.		
HWLBL75	766877	753	305 - 601	2013	Asn-28 to Thr-34.	S0374: 1 and L0731: 1.		
HWLBI01	919168	754	56 - 274	2014		S0374: 1 and L0748: 1.	7q22	126650, 126650, 154276, 173360, 173360, 602136, 602136, 602136, 602447
HWLAU04	953433	755	3 - 290	2015	Thr-12 to Thr-24.	L0763: 1 and S0374: 1.	5p15	123000, 600857
HWLAQ11	966207	756	77 - 214	2016		L0805: 3, L0738: 1 and S0374: 1.		
HWLAL10	971666	757	2 - 184	2017	Asp-4 to Pro-9.	L0662: 1 and S0374: 1.		
HWLAC70	775771	758	76 - 237	2018		S0374: 1 and L0744: 1.		
HWLAC29	690263	759	3 - 155	2019		L0748: 3 and S0374: 1.		
HWLAB74	765196	760	322 - 468	2020	Tyr-17 to Cys-22.	L0439: 5 and		

HWGQA42	713348	761	103 - 297	2021			S0374: 1.			
HWCAG11	966623	762	1 - 246	2022	Thr-30 to Glu-35.		S0382: 1 and L0744: 1.			
HWCAD06	886808	763	2 - 571	2023	Pro-19 to Gln-38, Ser-45 to Arg-50, Gly-135 to Lys-143, Arg-148 to Ser-156, Val-174 to Tyr-179.		S0294: 1, L0766: 1 and L0777: 1.			
HVATY05	928713	764	486 - 683	2024	Asn-37 to Gln-45, Leu-56 to Lys-66.		AR051: 11, AR054: 2, AR050: 1 S0294: 1			
HVASJ79	951617	765	3 - 638	2025			L0598: 2, L0752: 2, L0753: 2, L0364: 1, L0776: 1 and S0380: 1.			
HVAPI01	913930	766	323 - 490	2026	Met-4 to Trp-9, Phe-37 to Ser-43.		L0764: 1, S0380: 1 and L0749: 1.			
HVAET01	913958	767	32 - 145	2027			L0775: 1 and S0380: 1.			
HVAEP04	925914	768	2 - 172	2028			L0776: 1 and S0378: 1.			
HVACY04	926473	769	63 - 281	2029			L0663: 1 and S0378: 1.			
HUTSF11	966029	770	3 - 302	2030	Glu-1 to Glu-6, Asn-16 to Arg-22.		L0809: 1, S0378: 1, L0439: 1 and L0599: 1.			
							AR089: 0, AR061: 0 S0464: 1 and L0356: 1.			

HUTAF08	958353	771	197 - 391	2031	Thr-20 to Ala-28.	S0440: 1, L0779: 1 and L0758: 1.		
HUFGC48	950707	772	3 - 443	2032	Lys-32 to Trp-37, Asp-81 to Asn-88, His-93 to Leu-98.	L0589: 1 and H0506: 1.		
HUFFW06	934895	773	1 - 330	2033		L0747: 1 and H0506: 1.		
HUFFC02	969054	774	2 - 238	2034	Ala-37 to Arg-52.	L0590: 1 and H0506: 1.		
HUFDO11	966407	775	100 - 309	2035		H0506: 1.		
HUFDN22	783765	776	143 - 436	2036	Val-9 to Asp-17, Ile-55 to Tyr-60, Pro-69 to Asp-82, Asp-89 to Tyr-94.	L0777: 1 and H0506: 1.	15q13	103581, 146150, 218000, 227220, 601623, 601800, 601889, 602117
HUFDH29	689979	777	287 - 493	2037	Arg-57 to His-69.	L0439: 4, L0581: 1 and H0506: 1.		
HUFDB03	923561	778	144 - 473	2038		L0740: 2 and H0506: 1.		
HUFCD89	786817	779	141 - 257	2039		H0506: 1.		
HUFCD04	731462	780	1 - 171	2040		H0506: 1.		
HUFCD80	773161	781	468 - 821	2041	Glu-45 to Val-57.	L0362: 1 and H0506: 1.		
HUFBP22	582067	782	36 - 509	2042	Asp-66 to Ser-80, Thr-109 to Tyr-114,	AR050: 130, AR051: 121,	14q11.2	182600, 186880,

					Pro-145 to Asp-152.	AR054: 109 H0506: 1		190195, 190195, 222700, 600243, 602279, 602279
HUFBD16	661856	783	222 - 359	2043		L0748: 2 and H0506: 1.		
HUFAU90	787302	784	323 - 490	2044		L0756: 1 and H0506: 1.		
HUFAO77	772133	785	2 - 97	2045		L0439: 1 and H0506: 1.		
HUFAO24	467860	786	34 - 327	2046	Thr-11 to Cys-21, Ala-27 to Leu-32, Pro-56 to Gln-72.	L0757: 1 and H0506: 1.		
HUFAJ16	621443	787	757 - 467	2047		L0665: 1, L0745: 1 and H0506: 1.		
HUFAG52	727087	788	64 - 222	2048		UNKWN: 1, L0598: 1, L0766: 1, L0439: 1 and H0506: 1.		
HUFAB12	970725	789	3 - 281	2049	Thr-50 to Thr-93.	L0777: 2, L0769: 1, L0800: 1, L0740: 1 and H0506: 1.		
HTPHG02	918237	790	1 - 273	2050		H0622: 1, L0748: 1 and L0749: 1.		
HTPFS02	918251	791	2 - 271	2051	Gln-34 to Pro-41.	H0622: 1 and L0581: 1.		
HTPFF82	869864	792	135 - 440	2052	Pro-83 to Asn-88.	H0622: 1		

HTPFF81	869862	793	193 - 381	2053	Ser-2 to Phe-8.	H0622: 1		
HTPEI73	465462	794	3 - 269	2054	His-1 to Gln-9, Glu-11 to Ser-20, Ser-23 to Pro-49.	H0039: 1		
HTPDZ79	968067	795	3 - 611	2055	His-1 to Thr-7, Ile-45 to Ser-50, Ser-58 to Asp-63, Gly-66 to Gln-89, Leu-97 to Pro-114, Ser-126 to Phe-132, Lys-140 to Lys-145, Ser-156 to Glu-166.	L0439: 3, L0438: 2, H0039: 1 and L0748: 1.		
HTPDV49	931787	796	1501 - 1214	2056	Leu-18 to Asn-25.	H0039: 1		
	956048	1264	1108 - 1395	2524	Leu-18 to Asn-25, Leu-70 to Cys-76.			
HTPDA96	796101	797	99 - 302	2057	Glu-26 to Leu-33, Asn-51 to Arg-58, Val-61 to Cys-68.	H0039: 1 and L0756: 1.		
HTPCZ41	576943	798	3 - 431	2058		L0596: 4, H0039: 1, L0761: 1, L0659: 1 and L0809: 1.		
HTPCV43	459467	799	176 - 460	2059		H0039: 1, L0744: 1 and L0755: 1.		
HTPCS79	835550	800	1 - 390	2060		L0741: 3 and H0039: 1.		
HTPCR30	574757	801	26 - 241	2061		H0039: 1 and L0748: 1.		
HTPCE41	712642	802	1 - 420	2062		H0039: 1 and		



HTPBX04	927828	803	125 - 265	2063			L0766: 1. H0039: 1, L0438: 1 and L0439: 1.		
HTPBU39	530441	804	2 - 172	2064			H0039: 1		
HTPBU35	530440	805	1 - 366	2065		Ser-16 to Phe-24.	L0766: 5, H0039: 1, L0769: 1, L0774: 1, L0806: 1 and L0779: 1.		
HTPBD55	754147	806	169 - 2	2066		Lys-1 to Pro-7, Gln-46 to Lys-56.	H0039: 1, L0748: 1, L0749: 1 and L0596: 1.		
HTPAT20	668771	807	235 - 375	2067			H0039: 1 and L0603: 1.		
HTPAP93	791415	808	78 - 218	2068		Cys-32 to Gln-38.	H0039: 1 and L0581: 1.		
HTPAO01	961062	809	2 - 280	2069		Ile-13 to Thr-19.	L0758: 6, L0777: 2, H0039: 1, UNKWN: 1 and L0598: 1.		
HTPAI20	937644	810	2 - 418	2070		Thr-17 to Lys-32, Lys-45 to Gly-64, Glu-78 to Arg-91.	H0039: 1 and L0761: 1.		
HTPAG06	960784	811	3 - 230	2071		Leu-13 to Lys-30, Leu-36 to Ser-45, Gln-48 to Glu-69.	H0039: 1 and L0589: 1.		
HTPAE77	772737	812	286 - 534	2072		Val-7 to Leu-13.	H0039: 1 and L0362: 1.		
HTNTA60	840258	813	79 - 213	2073			L0601: 2 and		

HTNGF71	870037	814	195 - 368	2074	His-1 to Cys-7.	S0446: 1. L0592: 1 and S0456: 1.		
HSPMF55	871310	815	161 - 271	2075		H0479: 1 and L0756: 1.		
HSPMF20	575826	816	1 - 87	2076		H0479: 1		
HSPBD58	735472	817	296 - 457	2077	Ala-1 to Gly-6, Pro-19 to Asp-28, Lys-38 to Glu-54.	H0478: 1 and L0600: 1.		
HSPBC71	759886	818	658 - 903	2078		L0598: 4, UNKWN: 2, H0478: 1, L0748: 1 and L0754: 1.		
HSPAY58	964178	819	214 - 534	2079	Ser-29 to Leu-34, Leu-53 to Gly-62, Lys-80 to Asn-86, Ser-94 to Asp-99, Ile-102 to Lys-107.	AR054: 31, AR050: 25, AR051: 18 L0748: 2 and H0478: 1.		
HSPAI56	582583	820	1 - 261	2080	Ala-12 to Ala-37, Ser-47 to Glu-52, Ser-77 to Ser-87.	H0478: 1 and L0439: 1.		
HSPAI52	727212	821	99 - 395	2081	Phe-23 to Lys-29.	H0478: 1 and L0439: 1.		
HSPAB58	736098	822	3 - 116	2082	Ser-20 to Tyr-25.	AR089: 1, AR061: 0 H0478: 1, L0748: 1 and L0749: 1.		
HSODZ52	825096	823	89 - 298	2083		L0748: 1 and H0595: 1.		

HSODZ07	955932	824	245 - 505	2084	Thr-11 to Lys-23, Lys-45 to Gly-63.	AR061: 10, AR089: 5 H0595: 1		
HSODV84	782529	825	454 - 612	2085		L0745: 3 and H0595: 1.		
HSODU86	784754	826	3 - 149	2086		L0740: 2 and H0595: 1.		
HSODS38	709399	827	219 - 362	2087		L0748: 1 and H0595: 1.		
HSODR06	934645	828	1 - 234	2088		L0589: 2 and H0595: 1.		
HSODK89	786581	829	111 - 269	2089		L0754: 1 and H0595: 1.		
HSODH33	701833	830	76 - 267	2090	Ser-43 to Phe-57.	L0794: 1, L0756: 1 and H0595: 1.		
HSODE10	963727	831	166 - 327	2091	Arg-6 to Ile-11.	L0783: 1, L0747: 1, L0777: 1, L0759: 1 and H0595: 1.		
HSODD28	685884	832	67 - 222	2092	Phe-18 to Tyr-23, Tyr-35 to Asn-40, Arg-42 to Lys-52.	L0763: 1, L0754: 1 and H0595: 1.		
HSOBR45	717282	833	141 - 296	2093	Lys-1 to Asp-10.	L0749: 1 and H0595: 1.		
HSOBP04	871340	834	270 - 434	2094		L0766: 1 and H0595: 1.		
HSOBO01	882825	835	73 - 273	2095		L0748: 1 and H0595: 1.		
HSOBN03	923315	836	1 - 183	2096	Lys-5 to Pro-11,	L0777: 1, L0759:		

HSOBM53	727811	837	227 - 400	2097	Asn-23 to Leu-33.	1 and H0595: 1. L0749: 1 and H0595: 1.		
HSOBK75	766940	838	86 - 280	2098		L0756: 1 and H0595: 1.		
HSOBJ75	766949	839	252 - 434	2099	Leu-10 to Asn-18.	L0754: 1 and H0595: 1.		
HSOBH84	782118	840	20 - 133	2100	Ser-11 to Ser-16.	L0746: 1 and H0595: 1.		
HSOBF30	691440	841	331 - 534	2101	Arg-7 to Thr-13.	L0757: 2, L0717: 1, L0803: 1, L0805: 1, L0658: 1, L0809: 1, L0665: 1, L0740: 1, L0750: 1, L0779: 1, L0731: 1, L0758: 1 and H0595: 1.		
HSOBE61	908598	842	223 - 393	2102	Asn-42 to Asn-48.	AR089: 6, AR061: 2 L0766: 2, L0755: 1 and H0595: 1.		
HSOBE03	923322	843	261 - 362	2103		L0529: 2, L0543: 1, L0751: 1 and H0595: 1.		
HSOBC07	952409	844	217 - 417	2104		L0749: 1 and H0595: 1.		
HSOBB11	966281	845	2 - 97	2105		L0770: 1, L0748: 1 and H0595: 1.		
HSOAV63	745328	846	75 - 302	2106	Glu-2 to Trp-11.	L0748: 2 and H0343: 1.		

HSOAV11	967590	847	321 - 515	2107			L0805: 1 and H0343: 1.			
HSOAO64	746993	848	42 - 185	2108			L0754: 1 and H0343: 1.			
HSOAM10	968316	849	50 - 187	2109			H0343: 1 and L0591: 1.			
HSOAM07	953954	850	11 - 337	2110	Asn-7 to Arg-14, Arg-20 to Ser-26, Ser-60 to Glu-67, Thr-77 to Thr-84, Ser-91 to Glu-97.		L0758: 1 and H0343: 1.			
HSOAI35	537540	851	85 - 306	2111	Pro-29 to Ser-35, Pro-41 to Ser-49, Ser-62 to Arg-67.		L0439: 2, L0363: 1 and H0343: 1.			
HSOAG31	698357	852	160 - 306	2112			L0756: 1 and H0343: 1.			
HSOAF76	877300	853	2 - 217	2113	Gln-13 to Lys-20, Ala-24 to Cys-31.		L0749: 1 and H0343: 1.			
HSIGL32	698756	854	15 - 158	2114	Lys-1 to Tyr-16, Glu-41 to Gly-48.		H0590: 1 and L0439: 1.			
HSIGK77	771815	855	1 - 159	2115			H0590: 1 and L0581: 1.	9q34.1	103000, 114350, 120900, 131195, 185000, 189980, 600184, 602575, 602575	

HSIGK64	746241	856	261 - 422	2116	Ser-11 to Glu-16.	L0439: 2 and H0590: 1.		
HSIGJ94	793624	857	117 - 284	2117		AR061: 8, AR089: 7 H0590: 1, L0766: 1, L0659: 1, L0608: 1 and L0362: 1.		
HSIGG54	887545	858	3 - 461	2118	Ser-17 to Leu-25.	AR051: 4, AR050: 3, AR054: 1 H0590: 1		
HSIGG42	713339	859	151 - 363	2119	Arg-25 to Ser-31, Ala-54 to Pro-60.	H0590: 1 and L0746: 1.		
HSIGF42	866561	860	193 - 441	2120	Ala-13 to Ser-23.	H0590: 1 and L0438: 1.		
HSIGD15	659718	861	268 - 414	2121		L0748: 2, H0590: 1 and L0749: 1.		
HSIGA25	677668	862	347 - 487	2122		H0590: 1, L0774: 1 and L0751: 1.		
HSIFZ27	682580	863	35 - 265	2123	Gln-1 to Pro-16, Pro-61 to Asn-68.	H0590: 1 and L0748: 1.		
HSIFY57	734373	864	703 - 942	2124		H0590: 1, L0439: 1 and L0754: 1.		
HSIFV93	792005	865	210 - 383	2125		H0590: 1 and L0756: 1.		
HSIFV59	786436	866	105 - 488	2126	Gln-57 to Pro-63.	H0590: 1 and L0605: 1.		
HSIFR52	726370	867	3 - 305	2127	Lys-1 to Trp-10, Arg-57 to Val-62.	H0590: 1 and L0756: 1.		

HSIFL30	691630	868	3 - 113	2128			H0590: 1 and L0748: 1.		
HSIFK84	782810	869	2 - 493	2129	Pro-8 to Arg-15, Arg-20 to Gly-36, Asp-47 to Lys-54.		H0590: 1, L0745: 1 and L0750: 1.		
HSIFH19	668188	870	100 - 360	2130			H0590: 1 and L0748: 1.		
HSIFD30	691636	871	81 - 272	2131			L0777: 3, H0590: 1, L0766: 1, L0774: 1, L0789: 1, L0740: 1 and L0731: 1.		
HSIED64	747012	872	129 - 383	2132	Gly-1 to Ser-15.		H0036: 1 and L0747: 1.		
HSIED52	726017	873	16 - 252	2133	Asn-21 to Trp-28, Gln-68 to Ser-73.		L0747: 3 and H0036: 1.		
HSIEA68	753612	874	2 - 319	2134			H0036: 1, L0748: 1 and L0749: 1.		
HSIDZ18	666892	875	36 - 296	2135	Glu-1 to Ser-7.		H0036: 1 and L0608: 1.		
HSIDU10	866596	876	566 - 811	2136			H0036: 1		
HSIDS63	745340	877	211 - 291	2137			L0581: 2 and H0036: 1.		
HSIDQ95	795033	878	20 - 358	2138	Arg-1 to Asp-13, Glu-17 to Gln-29, Pro-58 to Gly-64, Pro-80 to His-89, Lys-100 to Lys-107.		H0036: 1, L0748: 1 and L0747: 1.		
HSIDH25	679296	879	137 - 229	2139			L0439: 2 and		

HSIDD63	559788	880	147 - 401	2140	Glu-14 to Met-25, Leu-29 to Lys-35, Ser-42 to Glu-47.	H0036: 1. H0036: 1 and L0605: 1.		
HSIDC85	783403	881	354 - 617	2141	Lys-1 to Leu-21.	H0036: 1 and L0749: 1.		
HSIDB51	725888	882	129 - 296	2142		H0036: 1 and L0748: 1.		
HSIDA48	721885	883	2 - 169	2143	Thr-35 to Val-41, Thr-47 to His-53.	L0599: 2 and H0036: 1.		
HSICV38	827957	884	105 - 386	2144	Asp-17 to Gly-25.	H0036: 1 and L0759: 1.		
HSICU58	507172	885	166 - 363	2145		AR050: 1, AR054: 0 H0036: 1		
HSICQ22	675004	886	296 - 490	2146	Gly-14 to His-20.	L0748: 2, H0036: 1 and L0758: 1.		
HSICP86	785733	887	55 - 339	2147		AR089: 1, AR061: 0 L0748: 2 and H0036: 1.		
HSICP22	586284	888	1 - 327	2148	Pro-26 to Tyr-37.	AR054: 11, AR050: 1, AR051: 1 H0036: 1		
HSIBB22	518673	889	32 - 160	2149		H0037: 1		
HSIAQ22	505052	890	222 - 365	2150	Ser-9 to Met-14.	H0036: 1 and L0665: 1.		



	510961	1265	366 - 256	2525	Ser-8 to Ser-14, Pro-19 to Cys-26.			
HSIAL16	496026	891	535 - 672	2151	Leu-7 to Leu-13.	L0748: 2 and H0036: 1.		
	866631	1266	208 - 366	2526				
HSIAL62	522231	892	203 - 367	2152	Val-20 to Ser-25.	H0036: 1		
HSIAL37	698015	893	2 - 73	2153		H0036: 1		
HSIAL03	960907	894	337 - 125	2154	Leu-1 to Lys-20.	L0771: 2, H0036: 1 and L0761: 1.		
HSIAD11	964915	895	2 - 139	2155	Arg-22 to Asp-37.	H0036: 1 and L0754: 1.		
HSIAB63	745637	896	100 - 333	2156	Glu-23 to Glu-32.	L0596: 2, L0604: 2 and H0036: 1.		
HSIAB05	932922	897	228 - 386	2157		H0036: 1 and L0608: 1.		
HSGBB01	916772	898	221 - 406	2158		H0447: 1, L0752: 1 and L0608: 1.	14q12-q13	135750, 160760, 160760, 182600, 600243, 600635, 600792, 601369, 602086, 602279, 602279
HSGAA12	971541	899	181 - 417	2159	Gly-2 to Arg-8, Ile-36 to Glu-41.	H0035: 1 and L0766: 1.		

HRTAR64	575020	900	78 - 248	2160	Leu-40 to Arg-48.	L0742: 2 and T0008: 1.		
HRTAR31	698417	901	176 - 322	2161	Lys-4 to Ile-10.	T0008: 1 and L0756: 1.		
HRTAP73	560932	902	201 - 61	2162	Phe-31 to Thr-42.	T0008: 1		
	867011	1267	266 - 499	2527	Glu-29 to Thr-35.			
HRTAN72	766328	903	3 - 260	2163	Pro-25 to Val-30.	T0008: 1		
HRTAN70	524889	904	24 - 230	2164		T0008: 1		
HRTAN65	753913	905	154 - 480	2165	Lys-62 to Lys-69.	T0008: 1, L0740: 1 and L0745: 1.		
HRTAN23	675124	906	101 - 208	2166		T0008: 1 and L0748: 1.		
HRTAE57	871385	907	165 - 401	2167		L0748: 2, T0008: 1 and L0754: 1.		
HRTAD37	708782	908	220 - 423	2168	Cys-38 to Thr-46, Lys-54 to Cys-61.	T0008: 1, L0471: 1, L0748: 1 and L0749: 1.		
HROEA53	838825	909	12 - 323	2169		H0598: 1 and L0439: 1.		
HROEA06	934673	910	93 - 254	2170		L0439: 3, L0745: 2 and H0598: 1.		
HRODY95	838830	911	211 - 333	2171		H0598: 1 and L0754: 1.	20	
HRODX43	949765	912	10 - 198	2172	Leu-2 to Ile-14.	H0598: 1 and L0756: 1.		
HRODU82	779482	913	5 - 565	2173	Ser-4 to Ser-12, Ser-30 to Trp-36, Ser-59 to Asn-67,	L0748: 54, L0581: 3, 4, H0598: 1 and L0756: 1.		

							Pro-69 to Ser-93, Pro-98 to Gly-112, Gly-119 to Gly-126.				
HRODE08	958532	914	381 - 608	2174			Ser-62 to Leu-73.			H0598: 1, L0387: 1 and L0805: 1.	
HRODD02	918978	915	3 - 422	2175			Phe-6 to Gly-11, Arg-50 to Glu-56, Tyr-67 to Val-80.			H0598: 1 and L0748: 1.	
HROCC67	751223	916	3 - 182	2176						L0754: 2 and H0316: 1.	
HROCC38	709348	917	60 - 179	2177			Ala-20 to Asp-25.			H0316: 1 and L0748: 1.	
HROCB26	812019	918	2 - 265	2178			Gln-1 to Asp-8, Glu-14 to Lys-29, Lys-44 to Gln-49.			H0316: 1 and L0747: 1.	
HROCA33	701847	919	418 - 284	2179			Cys-1 to Ala-9.			H0316: 1 and L0745: 1.	
HROBZ37	708773	920	142 - 294	2180						L0748: 4 and H0598: 1.	
HROBY02	918972	921	53 - 511	2181			Pro-21 to Asp-30.			H0598: 1 and L0761: 1.	
HROBW35	707622	922	223 - 378	2182						H0598: 1 and L0748: 1.	
HROBU31	693831	923	228 - 461	2183						H0598: 1, L0373: 1 and L0740: 1.	
HROBU02	951649	924	72 - 275	2184			Pro-31 to Pro-41, Pro-50 to Glu-57.			H0598: 1 and L0748: 1.	
HROBR02	918985	925	209 - 412	2185						H0598: 1 and	

HROBL46	718638	926	87 - 218	2186	Trp-2 to Met-7.	L0744: 1. H0598: 1 and L0748: 1.		
HROBH25	677574	927	390 - 542	2187		H0598: 1 and L0741: 1.		
HROBG67	751230	928	120 - 293	2188		H0598: 1 and L0748: 1.		
HROBF19	668013	929	191 - 430	2189	Ser-19 to Gln-25.	H0598: 1 and L0755: 1.		
HROBD79	774558	930	479 - 655	2190	Thr-15 to Ser-21.	L0748: 2 and H0598: 1.		
HROAZ07	973603	931	5 - 514	2191		AR089: 1, AR061: 0 H0316: 1		
HROAW79	774604	932	265 - 459	2192		H0316: 1 and L0754: 1.		
HROAV11	966329	933	22 - 189	2193	Lys-1 to Leu-6, Gln-9 to Lys-20.	H0316: 1 and L0748: 1.		
HROAU03	923381	934	205 - 339	2194		H0316: 1 and L0751: 1.		
HROAS95	795621	935	119 - 304	2195	Gly-25 to Lys-32.	H0316: 1 and L0596: 1.		
HROAS28	685982	936	248 - 382	2196		H0316: 1 and L0748: 1.		
HROAQ54	729168	937	246 - 353	2197		H0316: 1 and L0748: 1.		
HROAL96	867080	938	64 - 318	2198	Pro-15 to Gln-20, Ile-37 to Trp-47.	H0316: 1		

HROAJ83	781394	939	157 - 378	2199			H0316: 1 and L0748: 1.		
HROAI61	742084	940	1 - 609	2200			AR089: 4, AR061: 3 H0316: 1 and L0747: 1.		
HROAG39	526488	941	23 - 154	2201			H0316: 1		
HROAF96	830769	942	90 - 266	2202		Met-29 to Glu-46.	H0316: 1 and L0439: 1.		
HROAE84	881995	943	294 - 617	2203			H0316: 1		
HROAD39	597055	944	7 - 237	2204		Thr-23 to Glu-28.	H0316: 1 and L0754: 1.		
HROAD06	954694	945	126 - 443	2205		Glu-11 to Ser-19.	L0748: 2 and H0316: 1.		
HPASF63	745524	946	98 - 217	2206			H0270: 1 and L0748: 1.		
HPASE19	672016	947	70 - 258	2207			H0270: 1 and L0439: 1.		
HOCNF65	859585	948	217 - 405	2208		Gly-12 to Thr-19.	L0438: 2, L0742: 2, L0439: 2 and S0442: 1.		
HNSMD08	958337	949	251 - 499	2209			S0436: 1 and L0462: 1.		
HNSMC05	840216	950	255 - 554	2210		Ser-25 to Gln-30, His-38 to Asn-43.	L0753: 1 and S0436: 1.		
HNSAA51	971484	951	4 - 612	2211		Thr-1 to Gly-16, Gln-43 to Glu-50, Ser-136 to Gly-153,	AR089: 225, AR061: 197, AR050: 118,		

						Asn-169 to Phe-174, Thr-182 to Gln-188.	AR054: 115, AR051: 92 L0768: 1, L0666: 1 and S0434: 1.			
HNKCM03	922136	952	61 - 252	2212			L0803: 1 and S0330: 1.			
HNKAZ51	947067	953	31 - 612	2213		Arg-11 to Arg-18, Gln-96 to Gln-102, Gln-121 to Gln-128.	AR050: 2, AR061: 1, AR089: 0, AR054: 0, AR051: 0 L0015: 1 and S0330: 1.			
HNKAO08	955691	954	177 - 416	2214		Lys-12 to Arg-19, Glu-26 to Ser-33, Asp-44 to Asn-49, Arg-68 to Arg-76.	S0330: 1 and L0756: 1.			
HNKAB83	914959	955	318 - 476	2215			S0330: 1 and L0745: 1.			
HNJDR12	968978	956	174 - 461	2216		Val-20 to Arg-31, Gly-52 to Asn-59.	L0757: 4 and S0328: 1.			
HNJCE58	927451	957	261 - 458	2217			S0328: 1, L0745: 1 and L0731: 1.			
HNJBY05	928680	958	134 - 301	2218		Lys-9 to Phe-14.	S0328: 1 and L0748: 1.			
HNALB40	507439	959	350 - 481	2219			H0380: 1 and L0581: 1.			
HNALB10	968198	960	1 - 150	2220		Met-17 to Leu-40.	H0380: 1, L0776: 1 and L0759: 1.			
HNAAAE09	888913	961	239 - 460	2221		Glu-24 to Asp-31.	AR054: 16,			

									AR050: 9, AR051: 3 H0379: 1			
HMZME85	861084	962	176 - 550	2222					L0364: 1, S0350: 1 and L0740: 1.	1q25.1	145001, 150292, 208250, 600995, 601652	
HMZME57	734417	963	159 - 308	2223					S0350: 1 and L0603: 1.			
HMZMD49	722624	964	255 - 443	2224			Ile-1 to Asn-6.		S0350: 1 and L0747: 1.			
HMZAE53	868116	965	1 - 315	2225					L0362: 4 and S0332: 1.			
HMZAC09	625188	966	198 - 632	2226			Trp-1 to Phe-8, Ala-94 to Trp-108.		S0332: 1 and L0758: 1.			
HMZAA34	703755	967	486 - 626	2227			Ile-29 to Ile-35.		L0754: 2, L0662: 1 and S0332: 1.			
HLXNC18	973906	968	203 - 403	2228			Pro-34 to Trp-41, Arg-43 to Thr-50.		S0448: 1			
HLXNB04	926933	969	89 - 298	2229			Arg-34 to Ser-43.		L0748: 3 and S0448: 1.	3q		
HLQIF28	856619	970	1 - 306	2230			Arg-36 to Leu-45.		AR089: 10, AR061: 8 L0581: 3, H0632: 1 and L0748: 1.	20p12	112261, 176640, 176640, 176640, 236700, 601920	
HLQHD03	856624	971	33 - 266	2231			Pro-1 to Phe-7,		L0751: 2 and			

						Gln-26 to Gly-32, Ile-52 to Pro-67.		H0632: 1.		
HLQGZ73	856638	972	169 - 282	2232		Arg-1 to Pro-10.		L0745: 2, L0731: 2 and H0632: 1.		
HLQGU11	965781	973	691 - 873	2233				H0632: 1, L0800: 1, L0438: 1, L0748: 1 and L0759: 1.		
HLQGP25	893692	974	357 - 524	2234				H0632: 1		
HLQGP12	969516	975	718 - 918	2235		Glu-14 to Ile-20.		L0748: 3, L0749: 2, H0632: 1 and L0455: 1.		
HLQGA01	915066	976	53 - 313	2236		Arg-78 to Tyr-84.		L0749: 2, H0632: 1 and L0748: 1.		
HLQFS05	928264	977	3 - 134	2237		Ala-22 to Thr-39.		H0574: 1 and L0600: 1.		
HLQFQ08	961154	978	411 - 94	2238		Ser-87 to Met-93.		H0574: 1, L0639: 1 and L0776: 1.		
HLQFE53	856700	979	420 - 869	2239				H0574: 1 and L0758: 1.		
HLQEW11	966019	980	2 - 172	2240		Tyr-18 to Gln-23, Glu-28 to Phe-33.		L0757: 2, H0574: 1, L0761: 1 and L0664: 1.		
HLQEN12	969694	981	330 - 539	2241				H0574: 1 and L0666: 1.		
HLQEN07	856733	982	46 - 141	2242				H0574: 1 and L0547: 1.		
HLQEM06	934078	983	119 - 244	2243				H0574: 1 and L0662: 1.		



HLQED04	969543	984	3 - 227	2244		H0574: 1 and L0581: 1.		
HLQDV62	743401	985	2 - 136	2245	His-40 to Lys-45.	H0574: 1 and L0744: 1.		
HLQDV01	916190	986	182 - 415	2246		H0574: 1, L0748: 1 and L0779: 1.		
HLQDU64	746435	987	257 - 445	2247	Arg-20 to Ala-37.	H0574: 1 and L0743: 1.		
HLQDT89	786115	988	577 - 816	2248		L0748: 4 and H0574: 1.		
HLQDR89	972425	989	140 - 262	2249	Ser-6 to Ser-12.	H0574: 1		
HLQDR47	720145	990	3 - 155	2250	Ala-18 to Ser-23, Ser-39 to Gly-45.	H0574: 1 and L0754: 1.		
HLQDR15	660003	991	268 - 498	2251		H0574: 1 and L0749: 1.		
HLQDQ72	973258	992	1 - 243	2252	Arg-9 to Thr-18, Pro-25 to Glu-33, Ser-67 to Ile-72, Pro-74 to Cys-79.	H0574: 1		
HLQDP33	702276	993	125 - 286	2253	His-1 to Phe-6, Leu-28 to Ile-33.	H0574: 1 and L0596: 1.		
HLQDM72	761347	994	150 - 284	2254	Leu-30 to Trp-36.	H0574: 1 and L0748: 1.		
HLQDM03	923862	995	85 - 180	2255		H0574: 1 and L0747: 1.		
HLQDI01	916193	996	292 - 480	2256		H0574: 1 and L0766: 1.		
HLQDI75	856759	997	118 - 324	2257	Val-14 to Arg-24,	H0574: 1		

HLQDF69	754302	998	228 - 419	2258	Arg-31 to Asp-41.				
HLQDF27	682896	999	5 - 238	2259	Lys-1 to Trp-9. Pro-1 to Ala-8, Gln-27 to Gly-32, Val-37 to Gly-46, Leu-59 to Ala-66, Leu-73 to Gly-78.	H0574: 1 H0574: 1			
HLQDE32	707639	1000	348 - 578	2260		AR061: 7, AR089: 3 H0574: 1 and L0439: 1.			
HLQDC02	919611	1001	24 - 233	2261	Arg-10 to Ser-15, Arg-31 to Ala-36, Arg-64 to Gly-70.	L0757: 2, H0574: 1 and L0021: 1.			
HLQDB69	934462	1002	3 - 506	2262	Glu-1 to Ala-7, Pro-16 to Asp-22, Gln-27 to Glu-35.	H0574: 1 and L0745: 1.			
HLQCZ83	781052	1003	199 - 354	2263		H0574: 1 and L0749: 1.			
HLQCZ46	871684	1004	396 - 91	2264	Ser-7 to Thr-12.	L0439: 5, L0438: 3 and H0574: 1.			
HLQCY79	774827	1005	346 - 489	2265		L0748: 9 and H0574: 1.			
HLQCS58	735841	1006	3 - 134	2266	Arg-6 to Ser-14.	H0574: 1 and L0777: 1.			
HLQCQ09	625412	1007	1 - 144	2267		L0748: 2, H0574: 1 and L0777: 1.			
HLQCP89	689673	1008	583 - 762	2268		L0748: 2, H0574:			

HLQCO19	668521	1009	2 - 337	2269			1 and L0749: 1.		
HLQCK45	488499	1010	119 - 373	2270	Lys-47 to Lys-53.		L0748: 2 and H0574: 1.		
HLQCI96	823602	1011	135 - 401	2271	Glu-47 to Gly-53, Arg-55 to Val-64, Leu-69 to His-78.		L0748: 3, L0758: 2, H0574: 1 and L0591: 1.		
HLQCH67	751481	1012	91 - 282	2272	Glu-35 to Tyr-42, His-58 to Asn-64.		H0574: 1 and L0748: 1.	6	
HLQBS59	566772	1013	290 - 568	2273			L0748: 2 and H0574: 1.		
	868282	1268	276 - 560	2528			AR050: 10, AR054: 3, AR051: 1 H0331: 1		
HLQBQ19	671928	1014	171 - 299	2274			H0331: 1 and L0748: 1.		
HLQBF91	790408	1015	222 - 329	2275			H0331: 1 and L0748: 1.		
HLQBD38	948694	1016	34 - 192	2276	Gln-25 to Gly-35.		H0331: 1 and L0758: 1.		
HLQAX31	693626	1017	363 - 599	2277			L0756: 2 and H0331: 1.		
HLQAP90	787240	1018	289 - 107	2278	Glu-24 to Leu-31, Thr-34 to Gly-44.		H0331: 1 and L0599: 1.		
HLQAO31	698385	1019	25 - 204	2279			H0331: 1 and L0748: 1.		

HLQAN75	880815	1020	195 - 479	2280	Arg-27 to Gly-32.	L0748: 4 and H0331: 1.		
HLPBA84	912828	1021	349 - 549	2281		H0349: 1 and L0749: 1.		
HLICU57	871716	1022	2 - 238	2282	Ser-1 to Lys-7, Thr-19 to Glu-24.	H0355: 1 and L0749: 1.		
HLICS57	734450	1023	13 - 276	2283	Arg-14 to His-26, Gly-63 to Arg-70.	H0355: 1 and L0731: 1.		
HLICR28	686132	1024	2 - 235	2284	Asn-7 to Ser-13, Asn-25 to Lys-35, Thr-67 to Ser-72.	H0355: 1 and L0749: 1.		
HLICP76	825536	1025	300 - 518	2285		L0744: 3, H0355: 1 and L0756: 1.		
HLICO07	952625	1026	344 - 493	2286	Gly-1 to Thr-7, Gln-21 to Glu-29.	L0594: 2, H0355: 1, L0761: 1 and L0803: 1.		
HLICL82	779576	1027	3 - 203	2287	Asp-1 to Gly-6.	H0355: 1 and L0748: 1.		
HLICJ60	739746	1028	170 - 349	2288		L0749: 2, H0355: 1 and L0748: 1.		
HLIBZ10	963973	1029	99 - 338	2289	Lys-30 to Val-35.	H0355: 1 and L0748: 1.		
HLIBK17	662438	1030	249 - 416	2290	Ser-3 to Ser-19.	H0355: 1 and L0439: 1.		
HLIBB54	782180	1031	3 - 260	2291	Pro-1 to Arg-9.	H0355: 1 and L0750: 1.		
HLDRT92	791215	1032	209 - 412	2292		L0748: 2 and H0510: 1.		

HLD RP58	735731	1033	452 - 634	2293	Pro-16 to Asp-24.	H0510: 1 and L0753: 1.		
HLD QV07	952691	1034	282 - 452	2294		H0510: 1, L0438: 1 and L0439: 1.		
HLD QN90	857062	1035	12 - 161	2295	Glu-24 to Arg-33, Cys-37 to Val-42.	H0510: 1 and L0759: 1.		
HLD QH68	835571	1036	290 - 499	2296	Pro-17 to Arg-27, Val-52 to Glu-61.	H0510: 1 and L0589: 1.		
HLD QD92	552019	1037	3 - 218	2297		L0748: 2 and H0510: 1.		
HLD QC57	734475	1038	33 - 230	2298		L0758: 2 and H0510: 1.		
HLD PE31	697969	1039	90 - 221	2299	Thr-25 to Thr-30, Pro-32 to Phe-37.	L0748: 2, L0749: 2, H0510: 1 and L0809: 1.	109565, 109565, 142640, 165500, 228960, 261515, 600044, 600700	
HLD OX46	719023	1040	73 - 249	2300	Asn-3 to Thr-8, Gly-21 to Lys-35.	L0741: 2, H0510: 1 and L0592: 1.		
HLD OT85	784331	1041	244 - 480	2301	Arg-44 to Gly-50.	H0510: 1 and L0439: 1.		
HLD OS76	770016	1042	320 - 439	2302	His-1 to Trp-7, Gln-18 to Thr-25.	H0510: 1 and L0581: 1.		
HLD OM43	715254	1043	263 - 466	2303		L0748: 2, H0510: 1 and L0805: 1.		

HLDOK25	678063	1044	2 - 253	2304		H0510: 1 and L0483: 1.		
HLDOE06	922162	1045	153 - 1	2305	Gly-7 to His-17.	H0510: 1, L0372: 1 and L0766: 1.		
HLDOD83	724046	1046	649 - 167	2306		L0748: 2, H0510: 1 and L0581: 1.		
HLD0C67	689240	1047	69 - 332	2307	Thr-32 to Trp-41, Arg-55 to Tyr-61, Asp-83 to Gly-88.	H0510: 1 and L0600: 1.		
HLDNR75	767294	1048	155 - 310	2308	Arg-12 to Met-20, Gln-34 to Arg-52.	H0510: 1 and L0748: 1.		
HLDNR54	729853	1049	121 - 321	2309	Gln-62 to Lys-67.	H0510: 1		
HLDNL92	792694	1050	48 - 218	2310	Phe-8 to Asp-14, Pro-39 to Lys-57.	H0510: 1 and L0748: 1.		
HLDNL57	963552	1051	1 - 360	2311	Glu-1 to Ala-12, Asp-75 to Trp-80.	L0731: 2 and H0510: 1.		
HLDDY07	952751	1052	187 - 357	2312		H0509: 1 and L0748: 1.		
HLDDS06	934929	1053	74 - 244	2313	Gln-6 to Trp-30, Thr-41 to Asn-57.	H0509: 1 and L0794: 1.		
HLDCW15	705466	1054	222 - 413	2314		L0748: 4 and H0509: 1.		
HLDCU74	765307	1055	3 - 239	2315	Arg-5 to Phe-20, Glu-27 to Leu-37, Glu-51 to Glu-58, Lys-69 to Asp-79.	H0509: 1 and L0743: 1.		
HLDCOE01	916444	1056	156 - 308	2316		H0509: 1 and L0779: 1.		

HLDBW64	746545	1057	356 - 183	2317	Pro-23 to Thr-34.	H0509: 1 and L0748: 1.		
HLDBV65	764915	1058	193 - 402	2318		AR089: 23, AR061: 7 H0509: 1	5	
HLDBT71	760347	1059	464 - 691	2319	Leu-22 to Asn-27.	L0748: 3, L0596: 2, H0509: 1 and L0749: 1.		
HLDBN55	731734	1060	252 - 599	2320	Pro-4 to Ser-9, Arg-11 to Phe-18, Val-22 to Phe-46.	H0509: 1 and L0596: 1.		
HLDBN38	678424	1061	71 - 232	2321	Gly-5 to Pro-11, Ala-17 to Gly-35, Ile-39 to Arg-44.	H0509: 1, L0438: 1 and L0439: 1.		
HLDBN03	924100	1062	413 - 811	2322	Leu-11 to Glu-17.	L0439: 4, H0509: 1, L0748: 1 and L0777: 1.		
HLDBI09	625542	1063	185 - 448	2323	Pro-26 to Ala-39.	H0509: 1 and L0749: 1.		
HLDBE09	625554	1064	3 - 158	2324	Pro-6 to His-13.	H0509: 1		
HLDBD09	625551	1065	85 - 423	2325	Ala-41 to Gly-63.	H0509: 1		
HLDBD02	920039	1066	17 - 328	2326	His-1 to Arg-7, Val-14 to Gly-22, Gln-29 to Arg-36, Pro-58 to Gly-64, Lys-84 to Ser-100.	H0509: 1		
HLDBC10	964582	1067	287 - 466	2327	Ala-1 to Tyr-6, Asp-13 to Ser-18, Leu-21 to Val-27.	H0509: 1		

HLDBB21	713680	1068	2 - 376	2328	Ser-7 to Asp-15, Leu-24 to Leu-29, Thr-116 to Ile-122, Ala-1 to Cys-8.	AR089: 27, AR061: 19 H0509: 1 H0509: 1	16p11.2	147781, 172471, 182381
HLDBB08	959385	1069	1 - 117	2329		L0756: 3 and H0509: 1.		
HLDAV58	736027	1070	203 - 361	2330				
HLDAV38	709140	1071	147 - 344	2331	Val-1 to Tyr-6.	H0509: 1		
HLDAV13	657191	1072	224 - 439	2332	Ala-1 to Asp-8, Thr-27 to Arg-33.	H0509: 1		
HLDAV01	916462	1073	3 - 185	2333	Met-35 to Gln-41.	H0509: 1		
HLDAV12	970634	1074	163 - 324	2334	Gln-47 to Cys-53.	H0509: 1 and L0439: 1.		
HLDAK33	857107	1075	2 - 286	2335		L0617: 1 and H0509: 1.	22q11.23	123620, 600850
HLDAJ38	709138	1076	360 - 476	2336		H0509: 1 and L0748: 1.		
HLDA A31	586638	1077	2 - 235	2337		H0509: 1		
HKCTA23	877228	1078	171 - 305	2338	Phe-9 to Tyr-21.	L0754: 2 and H0205: 1.		
HISET33	974559	1079	98 - 430	2339	Gly-47 to Ser-65.	H0539: 1		
HISEQ03	923095	1080	227 - 412	2340	Ser-37 to His-45.	H0539: 1 and L0748: 1.		
HISEI01	915375	1081	2 - 397	2341	Leu-1 to Asn-9, His-51 to Asp-58, Pro-86 to Thr-97.	H0539: 1 and L0748: 1.		
HISEF78	841308	1082	442 - 762	2342		H0539: 1 and L0362: 1.		
HISDW49	928682	1083	991 - 149	2343	Asp-21 to Gly-26.	AR089: 5, AR061:		



								3 H0539: 1 and L0581: 1.		
HISDQ54	843345	1084	268 - 663	2344			Glu-38 to Pro-43.	H0539: 1 and L0596: 1.		
HISDL84	782286	1085	210 - 1	2345			Lys-60 to Asn-70.	H0539: 1 and L0439: 1.		
HISDF08	958417	1086	3 - 470	2346			Asn-10 to Arg-15, Arg-41 to Gly-48.	L0369: 1, H0539: 1 and L0608: 1.		
HISCQ82	975205	1087	474 - 710	2347			Ala-13 to Ser-22.	H0539: 1		
HISCO10	964285	1088	197 - 409	2348				H0539: 1		
HISCN94	794189	1089	200 - 760	2349			Glu-6 to Glu-19.	H0539: 1, L0439: 1 and L0756: 1.		
HISCH73	764281	1090	173 - 376	2350			Gly-16 to Val-22.	H0539: 1 and L0605: 1.		
HISCG55	731544	1091	723 - 1094	2351				L0439: 6, L0593: 2 and H0539: 1.		
HISCF69	882055	1092	1 - 405	2352			Thr-41 to Ala-48, Arg-57 to Gly-68, Pro-91 to Gly-98.	L0385: 1 and H0539: 1.		
HISCF31	950628	1093	137 - 424	2353			Asn-37 to Leu-52, Asn-79 to Ser-86.	H0539: 1 and L0749: 1.		
HISBZ83	781018	1094	161 - 433	2354			Gly-81 to Lys-91.	L0766: 1, H0539: 1 and L0602: 1.		
HISBW78	840252	1095	164 - 349	2355			Gln-31 to Asp-37.	L0622: 1 and H0539: 1.		
HISBV60	740184	1096	106 - 255	2356			Asp-44 to Thr-50.	H0539: 1 and L0362: 1.		

HISBV54	729356	1097	288 - 1	2357	Thr-30 to Trp-35.	H0539: 1 and L0589: 1.		
HISBU75	767166	1098	155 - 295	2358	Tyr-7 to Ser-13.	H0539: 1 and L0747: 1.		
HISBS95	795748	1099	285 - 446	2359		H0539: 1 and L0777: 1.		
HISBM13	656325	1100	315 - 449	2360		H0539: 1, L0740: 1 and L0599: 1.		
HISBM08	959051	1101	160 - 465	2361	Arg-15 to Glu-21, Ser-47 to Asp-63, Leu-85 to Ile-93.	L0769: 1 and H0539: 1.		
HISBK58	735838	1102	586 - 750	2362		H0539: 1 and L0754: 1.		
HISBH79	774837	1103	111 - 350	2363		H0539: 1 and L0603: 1.	16p13.3	141750, 141800, 141800, 141800, 141800, 141800, 141850, 141850, 141850, 141850, 141850, 156850, 186580, 191092, 600140, 600273, 601313,

HISBE17	662758	1104	42 - 251	2364	Ile-23 to Leu-31.	H0539: 1 and L0740: 1.	601785
HISBE11	966736	1105	86 - 223	2365		H0539: 1 and L0758: 1.	
HISAV01	857530	1106	5 - 211	2366	Asn-4 to Glu-13.	L0523: 1 and H0539: 1.	
HISAU80	775438	1107	124 - 273	2367		L0748: 4 and H0539: 1.	
HISAU79	774728	1108	11 - 142	2368	Gly-4 to Lys-10, Gln-36 to Asp-41.	H0539: 1	
HISAU67	751386	1109	1 - 156	2369	His-1 to Ser-10, Tyr-37 to Lys-44.	H0539: 1	
HISAU07	952941	1110	86 - 223	2370		H0539: 1	
HISAT10	964340	1111	240 - 371	2371	Asn-1 to Tyr-8.	L0545: 1 and H0539: 1.	
HISAR89	786749	1112	101 - 349	2372	Ser-41 to Arg-47.	L0777: 2, H0539: 1 and L0756: 1.	
HISAQ95	973368	1113	2 - 184	2373		H0539: 1	
HISAO49	722310	1114	33 - 377	2374	Ala-2 to Ser-35, Glu-37 to Ser-42, Ala-45 to Gly-59.	H0539: 1 and L0361: 1.	
HISAL91	790044	1115	322 - 450	2375		H0539: 1 and L0744: 1.	
HISAH27	682899	1116	576 - 728	2376		H0539: 1 and L0754: 1.	
HISAG10	964526	1117	108 - 269	2377	Asp-4 to Gly-20.	L0598: 2 and H0539: 1.	

HISAF02	917357	1118	326 - 508	2378	Lys-10 to Ile-17.	L0768: 1 and H0539: 1.		
HISAE12	949195	1119	207 - 416	2379		L0439: 3, L0438: 1 and H0539: 1.		
HISAD14	658409	1120	306 - 587	2380	Ser-38 to Gln-44, Gln-46 to Gly-52, Thr-59 to Lys-64.	L0438: 2, H0539: 1, L0439: 1 and L0592: 1.		
HISAB77	772155	1121	63 - 224	2381	Leu-26 to Leu-32, Leu-42 to Tyr-47.	H0539: 1		
HISAB69	755024	1122	180 - 317	2382	Pro-15 to Ile-20, Leu-41 to Asp-46.	H0539: 1		
HISAB54	728915	1123	145 - 423	2383	Glu-40 to Gly-45, Cys-47 to Glu-53.	L0439: 2 and H0539: 1.		
HISAB52	727115	1124	1 - 342	2384		H0539: 1		
HISAB28	686621	1125	2 - 112	2385	Thr-25 to Arg-30.	H0539: 1		
HISAB08	959335	1126	11 - 205	2386	Cys-18 to Val-33, Leu-60 to Arg-65.	H0539: 1		
HICAC35	707170	1127	127 - 333	2387		L0754: 1, L0755: 1 and S0384: 1.		
HHNAC01	913646	1128	513 - 722	2388		T0090: 1 and L0589: 1.		
HHNAB42	714097	1129	60 - 155	2389	Thr-1 to Trp-8, Pro-15 to Ser-20.	T0090: 1 and L0745: 1.		
HHLAB49	723222	1130	288 - 494	2390	Ser-35 to Pro-41, Pro-63 to Ser-69.	T0091: 1 and L0748: 1.		
HGODA23	675097	1131	9 - 233	2391		H0095: 1 and L0747: 1.		
HGBID78	772814	1132	248 - 463	2392	Gly-15 to Arg-21.	H0014: 1 and		

									L0605: 1.			
HGBHW16	662148	1133	186 - 290	2393					H0014: 1 and L0754: 1.			
HGBHV89	787037	1134	308 - 553	2394			Cys-77 to His-82.		H0014: 1 and L0740: 1.			
HGBHO02	954417	1135	110 - 406	2395					H0014: 1 and L0777: 1.	15q26	180090, 600318	
HGBHM39	705606	1136	244 - 483	2396			Ile-4 to Lys-10.		H0014: 1 and L0748: 1.			
HGBHM18	854310	1137	51 - 401	2397			Pro-21 to Trp-26, Ser-73 to Ser-78, Asp-105 to Trp-114.		H0014: 1 and L0752: 1.			
HGBHK55	713512	1138	282 - 515	2398			Asn-49 to Asn-59.		H0014: 1 and L0740: 1.			
HGBHG78	942445	1139	1 - 903	2399			Val-29 to Asp-35, Arg-121 to Thr-131, Pro-143 to Arg-148.		AR061: 8, AR089: 6 H0014: 1 and L0752: 1.			
HGBHE82	780030	1140	5 - 286	2400			Met-6 to Asn-18, Lys-20 to Pro-34, Gly-40 to Gln-57.		L0439: 2, H0014: 1 and L0435: 1.			
HGBHE68	753200	1141	225 - 437	2401					L0748: 2 and H0014: 1.			
HGBHD89	493910	1142	1 - 405	2402			Ser-61 to Pro-70, Gly-97 to Ala-103.		H0014: 1			
HGBHD52	812643	1143	84 - 329	2403					H0014: 1 and L0748: 1.			
HGBHB27	950174	1144	694 - 951	2404			Asn-1 to His-7,		L0770: 2, L0471:			

					Glu-14 to Ala-23, Pro-55 to Pro-69, Ala-79 to Gln-86.		1, H0014: 1 and L0779: 1.		
HGBGZ03	924788	1145	28 - 252	2405	Ala-32 to Ser-46.		H0014: 1 and L0751: 1.		
HGBGP21	671194	1146	363 - 569	2406	Lys-19 to Lys-25.		L0794: 2, L0749: 2, H0014: 1, L0770: 1, L0789: 1, L0438: 1, L0439: 1 and L0753: 1.		
HGBGM71	576919	1147	116 - 373	2407	Phe-14 to Met-25.		H0014: 1 and L0600: 1.		
HGBGL83	638178	1148	106 - 234	2408			H0014: 1		
HGBGL35	707128	1149	213 - 404	2409			H0014: 1 and L0605: 1.		
HGBGL19	671668	1150	319 - 462	2410			H0014: 1 and L0748: 1.		
HGBFP63	745487	1151	1 - 300	2411	Lys-20 to Val-31, Phe-34 to Glu-39, Thr-62 to Ala-69.		H0014: 1, L0745: 1 and L0750: 1.		
HGBEX85	784518	1152	125 - 238	2412			H0014: 1 and L0752: 1.		
HGBEX74	765894	1153	2 - 256	2413	Pro-1 to Thr-8.		L0748: 2, H0014: 1 and L0749: 1.		
HGBDY85	784615	1154	106 - 390	2414	Pro-42 to Gly-48, Lys-63 to Asp-69, Asp-88 to Lys-93.		H0014: 1 and L0766: 1.		
HGBDU06	960558	1155	1 - 501	2415	Arg-12 to Phe-18.		L0775: 3, H0014:		

								1, L0768: 1, L0774: 1, L0378: 1, L0783: 1, L0779: 1 and L0758: 1.			
HGBDM36	707917	1156	367 - 546	2416				L0766: 2 and H0014: 1.			
HGBDL39	710349	1157	418 - 573	2417		Ser-1 to Asp-6, Pro-15 to Ser-20.		L0748: 2 and H0014: 1.			
HGBDG15	660743	1158	2 - 172	2418				H0014: 1 and L0591: 1.			
HGBDG11	964929	1159	1 - 156	2419		Asn-1 to Lys-6, Asn-28 to Leu-35, Ser-38 to Arg-44.		H0014: 1 and L0657: 1.			
HGBCU53	871948	1160	231 - 431	2420				H0015: 1 and L0594: 1.			
HGBCS41	711528	1161	180 - 317	2421				H0015: 1 and L0747: 1.	12q13.1	126337, 600808, 601284, 601769, 601769, 602116	
HGBBP65	753956	1162	91 - 333	2422		Tyr-54 to Arg-62.		H0015: 1 and L0740: 1.			
HGBBG33	702930	1163	333 - 605	2423		Phe-8 to Gln-19, Arg-26 to Gly-32, Gln-50 to Cys-61.		H0015: 1 and L0747: 1.			
HGBBA50	578669	1164	227 - 364	2424		Pro-23 to Arg-29.		H0015: 1 and L0748: 1.			
HGBA177	772756	1165	164 - 397	2425		Leu-10 to Ser-22.		H0014: 1 and			

HGBAI59	868249	1166	345 - 569	2426	Arg-38 to Pro-49.	L0601: 1.			
HGBAC26	790172	1167	303 - 554	2427		H0014: 1 and L0581: 1.			
HGAMC08	958490	1168	2 - 349	2428	Lys-13 to Tyr-23, Cys-42 to Thr-52, Ser-71 to Pro-82, Lys-105 to Asn-112.	H0014: 1 and L0748: 1.			
HFVVC87	886358	1169	544 - 771	2429		S0408: 1 and L0764: 1.			
HFVJW07	951883	1170	295 - 516	2430	His-12 to Pro-25, Ser-45 to Gly-51, Asp-58 to Trp-67.	AR051: 34, AR050: 27, AR054: 24 H0393: 1			
HFVIP01	914567	1171	8 - 307	2431	Gly-1 to Glu-16, Pro-36 to Lys-45, Thr-50 to Pro-56.	L0777: 3 and H0393: 1.			
HFVID84	783129	1172	193 - 453	2432	Gly-22 to Gly-30, Tyr-53 to Pro-59, Ile-65 to Gly-70.	H0393: 1 and L0768: 1.			
HFVID08	959739	1173	142 - 516	2433	Pro-7 to Gln-20, Pro-25 to Pro-30, Gly-97 to Asp-106, Pro-109 to Arg-125.	H0393: 1 and L0439: 1.			
HFVIC84	783131	1174	440 - 147	2434	Lys-5 to Ile-16.	L0794: 2 and H0393: 1.			
						L0439: 2, L0749: 2, H0393: 1, L0744: 1 and L0750: 1.			



HFVIC30	881306	1175	3 - 452	2435	Tyr-15 to Leu-20.	H0393: 1 and L0581: 1.		
HFVHX74	854533	1176	173 - 409	2436	Pro-1 to Val-6, Pro-24 to Asn-32, Ser-49 to Gln-54.	H0393: 1 and L0591: 1.		
HFVHU23	676060	1177	375 - 512	2437	Glu-18 to Ser-24.	H0393: 1, L0779: 1 and L0777: 1.		
HFVHR05	932181	1178	188 - 358	2438	Thr-1 to Arg-6.	H0393: 1, L0742: 1 and L0748: 1.		
HFVHQ93	792444	1179	95 - 268	2439		H0393: 1, L0748: 1 and L0596: 1.		
HFVGY60	710929	1180	15 - 164	2440		H0393: 1		
	854540	1269	115 - 276	2529	Pro-42 to Ala-50.			
HFVGM12	971182	1181	221 - 328	2441		H0393: 1 and L0747: 1.		
HFVBA27	414543	1182	349 - 567	2442		L0748: 6, H0152: 3p21-p14. 1, L0749: 1, L0779: 1 and L0755: 1.	139330, 139360, 150250, 156845, 156845, 156845, 164500, 182280, 600163, 600971, 601226, 601267, 601373	
HFLVG70	757521	1183	36 - 455	2443		H0246: 1 and		

									L0749: 1.			
HFLUE23	676425	1184	90 - 248	2444	Ser-15 to Gln-22.				H0199: 1 and L0748: 1.			
HFLUE22	522779	1185	105 - 221	2445	Lys-7 to Phe-13.				H0199: 1			
HFLUD68	753847	1186	102 - 305	2446					H0199: 1 and L0749: 1.			
HFLQJ68	753216	1187	3 - 287	2447	Lys-7 to Leu-18.				H0357: 1 and L0745: 1.			
HFLQJ38	709034	1188	94 - 357	2448	Asp-17 to Asn-28, Gln-83 to Gln-88.				L0748: 2 and H0357: 1.			
HEPNE51	855589	1189	248 - 484	2449					S0430: 1 and L0750: 1.			
HDRMD24	676826	1190	57 - 257	2450	Ala-19 to Ser-28.				S0352: 1, L0438: 1 and L0748: 1.			
HDRMA68	785478	1191	2 - 214	2451	Gly-1 to Thr-11.				S0352: 1 and L0744: 1.			
HDRMA04	927372	1192	3 - 173	2452					L0731: 3, S0352: 1, L0771: 1 and L0605: 1.			
HDDAF49	911314	1193	144 - 320	2453	Glu-15 to Ser-24.				AR061: 9, AR089: 3 H0339: 1			
HDDAE06	954683	1194	309 - 494	2454	Arg-8 to Thr-14.				L0748: 2 and H0339: 1.			
HDDAC56	733673	1195	2 - 166	2455	Tyr-19 to Ile-36.				H0339: 1 and L0754: 1.			
HDDAC11	840301	1196	65 - 190	2456	Ser-19 to Thr-32.				H0339: 1 and L0754: 1.			

HDDAB07	954150	1197	165 - 260	2457		H0339: 1, L0526: 1 and L0518: 1.		
HCYBO59	520114	1198	68 - 385	2458	Glu-19 to Arg-32, Glu-54 to His-78, Ser-84 to Gly-95.	T0114: 1 and L0748: 1.		
HCYBL79	888275	1199	374 - 144	2459	Leu-9 to His-16.	L0779: 2 and T0114: 1.		
HCRQB03	922880	1200	274 - 546	2460	Asp-18 to Asn-26, His-28 to Gly-36, Cys-67 to Gln-78.	S0356: 1 and L0772: 1.		
HCRPQ40	881408	1201	641 - 495	2461	Phe-29 to Lys-34.	L0517: 2, S0356: 1, L0021: 1, L0527: 1, L0745: 1 and L0758: 1.		
HCRPE30	910021	1202	49 - 123	2462		S0356: 1		
HCROA43	948286	1203	1 - 810	2463		AR050: 40, AR054: 32, AR051: 32, AR061: 1, AR089: 1, S0356: 1		
HCRNR03	922819	1204	1 - 456	2464		L0752: 2, S0356: 1, L0766: 1, L0438: 1 and L0439: 1.		
HCRND06	934631	1205	2 - 235	2465		S0356: 1, L0803: 1, L0774: 1, L0776: 1, L0438: 1, L0439: 1 and L0759: 1.		
HCRMX10	963663	1206	86 - 409	2466	Lys-1 to Pro-19,	L0776: 3, S0356: 1		

							Phe-23 to Lys-28, Gly-35 to Trp-42, Ala-50 to Leu-57, Ala-102 to His-107.	1, L0805: 1 and L0757: 1.			
HCRMGI1	965918	1207	12 - 284	2467				S0356: 1 and L0779: 1.			
HCQDE22	949991	1208	218 - 745	2468			Ile-132 to Gly-138, Phe-149 to Thr-154.	AR061: 6, AR089: 2 H0596: 1 and L0749: 1.			
HCQDA13	908299	1209	225 - 422	2469			Phe-26 to Asn-33.	L0748: 2, H0596: 1 and L0776: 1.			
HCQCQ76	953491	1210	199 - 411	2470				L0777: 2, H0596: 1, L0768: 1 and L0756: 1.			
HCQAC71	951844	1211	240 - 443	2471			Ser-16 to Cys-22, Pro-35 to Cys-44.	H0263: 1 and L0759: 1.			
HCNSR78	773818	1212	64 - 159	2472				H0231: 1 and L0748: 1.			
HCNSR32	699694	1213	307 - 74	2473			Glu-9 to Glu-14, Thr-31 to Lys-39.	L0754: 2 and H0231: 1.			
HCNSE03	925492	1214	528 - 713	2474			Arg-15 to Lys-20, His-42 to Lys-53.	L0766: 2, H0231: 1, L0768: 1, L0794: 1 and L0749: 1.			
HCNDV73	764119	1215	190 - 294	2475				H0597: 1 and L0745: 1.			
HCNDV41	862324	1216	3 - 296	2476				H0597: 1, L0369: 1 and L0666: 1.			

HCNDK37	706359	1217	27 - 293	2477	Leu-1 to Leu-10, Ser-34 to Lys-39.	H0597: 1 and L0747: 1.		
HCNDF65	747499	1218	169 - 369	2478	Glu-2 to Gln-9, Arg-46 to Arg-51.	H0597: 1 and L0748: 1.		
HCNDB86	785168	1219	187 - 519	2479	Ile-4 to Pro-10.	H0597: 1 and L0748: 1.		
HCNCX91	789556	1220	46 - 189	2480		H0597: 1 and L0748: 1.		
HCNCX27	682479	1221	322 - 483	2481	Asp-31 to Phe-36, Thr-42 to Glu-47.	L0599: 2 and H0597: 1.		
HCNCT03	923344	1222	334 - 429	2482		H0597: 1 and L0607: 1.		
HCNCO59	738889	1223	2 - 229	2483	Lys-60 to Val-65.	H0597: 1 and L0748: 1.		
HCNCM79	892693	1224	174 - 428	2484	His-25 to Leu-30, Lys-52 to Ser-59, Pro-73 to Ser-79.	H0597: 1 and L0764: 1.		
HCNCF19	668043	1225	244 - 465	2485		L0777: 3, L0748: 2, H0597: 1, L0776: 1, L0749: 1 and L0753: 1.		
HCNAZ20	670031	1226	114 - 257	2486	Pro-6 to Phe-12.	L0517: 3, H0085: 1 and L0748: 1.		
HCNAY45	716992	1227	56 - 382	2487	His-27 to Arg-32.	L0745: 2, H0085: 1, L0367: 1, L0748: 1 and L0439: 1.		
HCNAT92	518899	1228	1 - 243	2488	Asn-1 to Glu-8, Thr-14 to Ser-21.	H0085: 1		

						Gln-38 to Phe-45, Gly-48 to Glu-55.				
HCNAT67	508295	1229	155 - 274	2489					H0085: 1	
HCNAQ26	685199	1230	408 - 548	2490		Thr-7 to Glu-13.			H0085: 1 and L0604: 1.	
HCNAP29	855685	1231	1 - 255	2491		His-14 to Gln-19.			H0085: 1 and L0766: 1.	
HCNAL30	522672	1232	3 - 83	2492		Arg-10 to Gln-20.			H0085: 1	
HCNAK11	967945	1233	61 - 204	2493		Leu-26 to Asp-32, Gly-37 to Ala-48.			H0085: 1, L0748: 1, L0749: 1 and L0758: 1.	
HCNAA41	791545	1234	183 - 572	2494					H0085: 1 and L0749: 1.	
HCLHE01	914341	1235	436 - 633	2495					L0740: 2, H0676: 1, L0371: 1, L0748: 1 and L0608: 1.	
HCIAD89	786766	1236	525 - 325	2496					H0489: 1, L0741: 1 and L0756: 1.	
	862441	1270	155 - 451	2530		Lys-5 to Lys-15, Phe-48 to Trp-61.				
HCIAC12	970750	1237	158 - 661	2497		Gln-1 to Gln-15.			L0772: 3, H0489: 1 and L0764: 1.	
HASMC23	675527	1238	53 - 247	2498					L0756: 1 and S0394: 1.	
HAQNH18	883367	1239	2 - 313	2499					L0439: 3, L0438: 1 and S0392: 1.	
HAQNB68	752573	1240	2 - 289	2500		Phe-34 to Val-45.			S0392: 1 and L0748: 1.	

HAQMP04	925685	1241	338 - 742	2501	Cys-47 to Asn-53.	L0794: 2 and S0392: 1.		
HAQMK53	727708	1242	16 - 180	2502		S0392: 1 and L0748: 1.		
HALTA38	705895	1243	250 - 444	2503	Asn-1 to Glu-6.	L0361: 2, H0147: 1 and L0731: 1.		
HALSD90	500844	1244	70 - 171	2504		H0098: 1		
HALSD51	500852	1245	186 - 329	2505		H0098: 1		
HALSD34	509765	1246	42 - 188	2506		H0098: 1		
HALSD03	960910	1247	2 - 178	2507		H0098: 1		
HALSC37	705894	1248	1 - 195	2508		H0098: 1		
HALSC18	667044	1249	62 - 277	2509	Ala-13 to Arg-25, Asn-33 to Lys-41.	H0098: 1		
HAJRA03	923504	1250	3 - 122	2510		L0777: 2, S0306: 1, L0519: 1 and L0756: 1.		
H2MCA78	575194	1251	26 - 370	2511	Gly-8 to His-17.	L0754: 2 and T0109: 1.		
H2MBY07	953691	1252	23 - 190	2512	Gln-26 to Gln-31.	L0751: 2, H0656: 1, T0109: 1, L0804: 1, L0806: 1, H0658: 1 and L0758: 1.		
H2MBW43	715430	1253	114 - 287	2513	Ser-11 to Glu-16.	T0109: 1 and L0748: 1.		
H2MBW31	698281	1254	105 - 332	2514	Ser-27 to His-32.	T0109: 1 and L0748: 1.		
H2MBH48	908926	1255	103 - 411	2515	His-17 to Lys-26, Gln-47 to Glu-53, 6	AR089: 6, AR061: 6		

					His-78 to Ala-85.	T0109: 1 and L0601: 1.			
H2MBE37	597070	1256	349 - 597	2516	Asp-1 to Asp-20, Leu-44 to Asn-51.	T0109: 1 and L0439: 1.			
H2MBA41	711567	1257	37 - 468	2517		T0109: 1, L0771: 1, L0809: 1 and L0742: 1.			
H2LAM15	767606	1258	3 - 584	2518		T0115: 1, L0769: 1 and L0786: 1.			
H2CBP41	923006	1259	51 - 515	2519	Arg-6 to Thr-12.	L0747: 2 and T0110: 1.			



[065] The first column in Table 1A provides a unique "Clone ID NO:Z" for a cDNA clone related to each contig sequence disclosed in Table 1A. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods known in the art and/or as described elsewhere herein.

[066] The second column in Table 1A provides a unique "Contig ID" identification for each contig sequence. The third column provides the "SEQ ID NO:X" identifier for each of the digestive system associated contig polynucleotide sequences disclosed in Table 1A. The fourth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1A, column 5, as SEQ ID NO:Y. Where the nucleotide position number "To" is lower than the nucleotide position number "From", the preferred ORF is the reverse complement of the referenced polynucleotide sequence.

[067] The fifth column in Table 1A provides the corresponding SEQ ID NO:Y for the polypeptide sequence encoded by the preferred ORF delineated in column 4. In one embodiment, the invention provides an amino acid sequence comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by "ORF (From-To)". Also provided are polynucleotides encoding such amino acid sequences and the complementary strand thereto.

[068] Column 6 in Table 1A lists residues comprising epitopes contained in the polypeptides encoded by the preferred ORF (SEQ ID NO:Y), as predicted using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, at least one, two, three, four, five or more of the predicted epitopes as described in Table 1A. It will be appreciated that depending on

the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

[069] Column 7 in Table 1A provides an expression profile and library code: count for each of the contig sequences (SEQ ID NO:X) disclosed in Table 1A, which can routinely be combined with the information provided in Table 4 and used to determine the normal or diseased tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in column 7 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. For those identifier codes in which the first two letters are not "AR", the second number in column 7 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of  $^{33}\text{P}$  dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. The sequences disclosed herein have been determined to be predominantly expressed in digestive

system tissues, including normal and diseased digestive system tissues (See Table 1A, column 7 and Table 4).

[070] Column 8 in Table 1A provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

[071] A modified version of the computer program BLASTN (Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish et al., Nat. Genet. 3:266-272 (1993)) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1A under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

[001] Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIM™ (*supra*). If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 9, Table 1A, labeled "OMIM Disease Reference(s)". Table 5 is a key to the OMIM reference identification

numbers (column 1), and provides a description of the associated disease in Column 2.

**TABLE 1B**

Clone ID NO:Z	SEQ ID NO:X	CONTIG ID:	BAC ID: A	SEQ ID NO:B	EXON From-To
H2CBG54	11	893910	AL359207	2531	1-130 251-698 740-817 3930-4391 4529-4618 5450-5960 6657-6857 6961-7270 7461-7497 7543-7643 7880-8245 8742-9344 9648-9948 10669-11177 11678-11844 12187-12724
H2CBG54	11	893910	AL359207	2532	1-958
H2MBV93	12	686344	AL031847	2533	1-34 414-908 1145-1972 6128-6273 6543-6675
HALSC22	13	503082	AC013783	2534	1-325
HALSC22	13	503082	AC013783	2535	1-319
HALSC22	13	503082	AL354797	2536	1-325
HALSC22	13	503082	AC068485	2537	1-188 1825-2174 3023-3181 4591-4915
HALSC22	13	503082	AC013740	2538	1-325
HALSC22	13	503082	AL354797	2539	1-159
HALSC22	13	503082	AC068485	2540	1-491
HALSC22	13	503082	AL354797	2541	1-490
HALSC22	13	503082	AC068485	2542	1-230 285-410
HALSC22	13	503082	AC013740	2543	1-490
HALSG01	15	500834	AC025008	2544	1-68 166-273 1178-1509

					1893-2197 3086-3625 4073-4342 4657-4797 5553-5905 6891-6945
HALSG01	15	500834	AC027052	2545	1-68 166-273 1178-1509 1893-2197 3086-3625 4106-4342 4657-4797 5553-5905 6891-6945
HALSG01	15	500834	AL365187	2546	1-105 586-822 1137-1277 2033-2385 3371-3425
HALSG01	15	500834	AC025008	2547	1-335
HALSG01	15	500834	AC027052	2548	1-335
HALSG01	15	500834	AL365187	2549	1-417
HALSJ15	17	501008	AF127936	2550	1-496
HALSJ15	17	501008	AF127936	2551	1-182
HALSJ15	17	501008	AF127936	2552	1-337
HALSK15	18	501003	AL138726	2553	1-142 971-1066 2195-2893
HALSL45	19	723542	AC025712	2554	1-1822 1892-2371
HALSN27	20	509759	AL357077	2555	1-151 2431-2753
HALSN27	20	509759	AL358777	2556	1-151 2431-2753
HCNAC10	25	968738	AL353678	2557	1-154 1195-1580 1587-2168 3515-3965 5140-5394 7947-8128 8641-8755 9183-9557
HCNAC10	25	968738	AC009657	2558	1-275
HCNAC10	25	968738	AL137849	2559	1-154 1195-1580 1587-2168

					3514-3964 5139-5408 7946-8127 8640-8754 9182-9556
HCNAC10	25	968738	AC009657	2560	1-182 696-774
HCNAG07	26	954493	AL359254	2561	1-332
HCNAG07	26	954493	AL359254	2562	1-399
HCNAG07	26	954493	AL359254	2563	1-153
HCNAK56	27	832249	AC023479	2564	1-256
HCNAK56	27	832249	AL136231	2565	1-256
HCNAK56	27	832249	AC023479	2566	1-258
HCNAK56	27	832249	AL136231	2567	1-258
HCNAK56	27	832249	AL136231	2568	1-644 709-2929 5175-6204 6371-6565 9803-10051 10520-10645 11191-11216
HCNAL66	28	832247	AC011747	2569	1-755
HCNAL66	28	832247	AC021669	2570	1-692
HCNAL66	28	832247	AC011747	2571	1-206 266-796 6613-6752 7056-7340
HCNAL66	28	832247	AC011747	2572	1-2511
HCNAL66	28	832247	AC021669	2573	1-206 266-796 6613-6752 7056-7340
HCNAN69	29	655816	AC068589	2574	1-318
HCNAN69	29	655816	AC009675	2575	1-318
HCNAN69	29	655816	AC009675	2576	1-520
HCNAO20	30	832251	AC073219	2577	1-123 288-775 1530-1839 1877-2491 2744-2824 3483-3563 3679-3881
HCNAO20	30	832251	AC073219	2578	1-169
HCNAO20	30	832251	AC073219	2579	1-552 560-881
HCNAR21	31	948746	AC073645	2580	1-421
HCNAR21	31	948746	AP002392	2581	1-421

HCNAR21	31	948746	AC006595	2582	1-421
HCNAR21	31	948746	AP002392	2583	1-187
HCNAR21	31	948746	AC006595	2584	1-187
HCNAR21	31	948746	AP002392	2585	1-200
HCNAR21	31	948746	AC006595	2586	1-200
HCNCH64	34	922009	AL161457	2587	1-279
HCNCH64	34	922009	AC025021	2588	1-279
HCNCH64	34	922009	AL161457	2589	1-1531
HCNCN84	35	766990	AC074373	2590	1-270
HCNCN84	35	766990	AC024952	2591	1-270
HCNCN84	35	766990	AC025594	2592	1-269
HCNCQ79	37	832242	AC022532	2593	1-523
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HDRMA68	1191	785478	AC005848	4916	1-164 343-428 578-2903 3020-3168 4072-4415 5074-5526 5547-5780
HDRMA68	1191	785478	AC005848	4917	1-863 1241-1590 1666-2167 2328-2424 2500-2950 3000-3341 3351-3962 3976-3995 4276-5430 5485-5585 5616-5892 6622-6727 7156-8018
HDDAF49	1193	911314	AC068243	4918	1-910

HDDAF49	1193	911314	AC068243	4919	1-474
HDDAE06	1194	954683	AL139012	4920	1-882
HDDAE06	1194	954683	AL139012	4921	1-634
HDDAE06	1194	954683	AL139012	4922	1-277
HDDAC56	1195	733673	AC012443	4923	1-558
HDDAB07	1197	954150	AC026075	4924	1-561
HDDAB07	1197	954150	AC026075	4925	1-516
HCYBL79	1199	888275	AL162261	4926	1-454
HCYBL79	1199	888275	AC015618	4927	1-453
HCYBL79	1199	888275	AL356957	4928	1-2000 2791-3036
HCYBL79	1199	888275	AL358813	4929	1-154 168-272 2427-2570 3307-3955 4488-4638 4640-5508 5813-6298 6577-8556
HCYBL79	1199	888275	AC018593	4930	1-154 168-272 2428-2571 3308-3956 4489-4639 4641-5509 5814-6299 6578-8557
HCYBL79	1199	888275	AC024468	4931	1-269 2419-2560 3305-3786 4474-5582 5736-6454 6554-8813 9717-9903
HCYBL79	1199	888275	AL354666	4932	1-455
HCYBL79	1199	888275	AL162612	4933	1-155 168-272 2427-2570 3309-3957 4477-4628 4630-4944 4986-5499 5827-6313 6597-8596 9375-9620
HCYBL79	1199	888275	AL355800	4934	1-453
HCYBL79	1199	888275	AL137798	4935	1-455

HCYBL79	1199	888275	AL021920	4936	1-455
HCYBL79	1199	888275	AL355149	4937	1-454
HCYBL79	1199	888275	AC021338	4938	1-446
HCYBL79	1199	888275	AL137802	4939	1-454
HCYBL79	1199	888275	AL356957	4940	1-379
HCYBL79	1199	888275	AL358813	4941	1-246
HCYBL79	1199	888275	AL162261	4942	1-901 1073-1200 1220-1344 1713-2288
HCYBL79	1199	888275	AC018593	4943	1-579
HCYBL79	1199	888275	AC015618	4944	1-475 1079-1217 1702-2277
HCYBL79	1199	888275	AL356957	4945	1-485
HCYBL79	1199	888275	AL358813	4946	1-579
HCYBL79	1199	888275	AC018593	4947	1-246
HCYBL79	1199	888275	AC024468	4948	1-478
HCYBL79	1199	888275	AL354666	4949	1-376
HCYBL79	1199	888275	AC024468	4950	1-835
HCYBL79	1199	888275	AL162612	4951	1-379
HCYBL79	1199	888275	AL162612	4952	1-579
HCYBL79	1199	888275	AL355800	4953	1-474 1078-1216 1701-2276
HCYBL79	1199	888275	AL137798	4954	1-266
HCYBL79	1199	888275	AL137798	4955	1-376
HCYBL79	1199	888275	AL021920	4956	1-266
HCYBL79	1199	888275	AL021920	4957	1-376
HCYBL79	1199	888275	AL355149	4958	1-474 1082-1212 1700-2275
HCYBL79	1199	888275	AC021338	4959	1-716
HCYBL79	1199	888275	AL137802	4960	1-474 1082-1212 1700-2275
HCRQB03	1200	922880	AC011676	4961	1-574
HCRQB03	1200	922880	AC011676	4962	1-198
HCRPQ40	1201	881408	AC055713	4963	1-110 2616-2733 4199-6427
HCRPQ40	1201	881408	AC048340	4964	1-2230
HCRPQ40	1201	881408	AC055713	4965	1-247
HCRPQ40	1201	881408	AC048340	4966	1-118
HCRPQ40	1201	881408	AC055713	4967	1-105
HCRPQ40	1201	881408	AC048340	4968	1-246

HCROA43	1203	948286	AC074373	4969	1-55 130-242 323-415 1103-1284 1397-1478 1831-2026 2418-3008
HCROA43	1203	948286	AC074373	4970	1-303
HCRNR03	1204	922819	AL139181	4971	1-43 946-1000 1203-1650 2360-2851
HCRNR03	1204	922819	AL138695	4972	1-43 946-1000 1203-1650 2360-2815
HCRNR03	1204	922819	AL139185	4973	1-43 946-1000 1203-1650 2360-2851
HCRNR03	1204	922819	AL139185	4974	1-618
HCRNR03	1204	922819	AL139181	4975	1-618
HCRMX10	1206	963663	AC009093	4976	1-372 720-1405
HCRMX10	1206	963663	AC009130	4977	1-372 720-1405
HCRMX10	1206	963663	AC007615	4978	1-372 720-1405
HCRMX10	1206	963663	AC009093	4979	1-1003
HCRMX10	1206	963663	AC007615	4980	1-1003
HCQDA13	1209	908299	AP001574	4981	1-391 399-934 989-1474 1539-1808 1878-2473 2611-3878 4484-4887 5018-5164 6084-6248 6329-7340 7770-8529 10244-10365 10679-10999 11721-11928 12212-12605 12918-13928
HCQDA13	1209	908299	AC013608	4982	1-1010



					1069-1262 1990-2258 2842-5055
HCQDA13	1209	908299	AF235095	4983	1-151 465-782 1507-1714 1998-2391 2704-3714 3773-3952 4694-4962 5546-6784
HCQDA13	1209	908299	AC013608	4984	1-377
HCQDA13	1209	908299	AF235095	4985	1-760
HCQDA13	1209	908299	AP001574	4986	1-422
HCQDA13	1209	908299	AC013608	4987	1-394
HCQCQ76	1210	953491	AC027326	4988	1-1321 1363-2417
HCQCQ76	1210	953491	AC010622	4989	1-1315 1357-1981
HCQCQ76	1210	953491	AC027326	4990	1-225
HCQCQ76	1210	953491	AC010622	4991	1-3115
HCQAC71	1211	951844	AC018845	4992	1-111 281-657 1134-1623 1791-1965 3712-4015 6018-6383 7498-7672 9645-9802 9952-10439 12178-12300 13340-13871 14159-14747 14949-16552
HCQAC71	1211	951844	AC007338	4993	1-111 281-657 1134-1613 1791-1965 3712-4015 6018-6383 7498-7672 9645-9802 9952-10439 12178-12300 13340-13871 14159-14747 14949-16552

HCQAC71	1211	951844	AC018845	4994	1-150
HCQAC71	1211	951844	AC007338	4995	1-150
HCNSR78	1212	773818	AL357078	4996	1-551
HCNSR78	1212	773818	AC025866	4997	1-551
HCNSR78	1212	773818	AL357078	4998	1-333
HCNSR78	1212	773818	AC025866	4999	1-333
HCNSR32	1213	699694	AC073041	5000	1-413
HCNSR32	1213	699694	AC073041	5001	1-538
HCNSR32	1213	699694	AC073041	5002	1-286
HCNSE03	1214	925492	AC026347	5003	1-954
HCNSE03	1214	925492	AC026347	5004	1-1101
HCNDV73	1215	764119	AC019310	5005	1-83 3708-4178 4287-4409 5057-5168 7946-8131 8252-8642 8735-9237 9607-9740 9794-10471 11799-12500
HCNDV73	1215	764119	AC019310	5006	1-371
HCNDV73	1215	764119	AC019310	5007	1-361
HCNDV41	1216	862324	AC024315	5008	1-627
HCNDV41	1216	862324	AL391001	5009	1-623
HCNDV41	1216	862324	AL391001	5010	1-268
HCNDV41	1216	862324	AC024315	5011	1-268
HCNDF65	1218	747499	AL161911	5012	1-1368
HCNDF65	1218	747499	AL354792	5013	1-3635 3862-4159 4318-4904 6635-7084 7088-8048
HCNDF65	1218	747499	AL161911	5014	1-298
HCNDF65	1218	747499	AL354792	5015	1-532
HCNDF65	1218	747499	AL354792	5016	1-2620
HCNDB86	1219	785168	AC026268	5017	1-548
HCNDB86	1219	785168	AC026268	5018	1-226
HCNCX91	1220	789556	AC009528	5019	1-1122
HCNCX91	1220	789556	AC009528	5020	1-309
HCNCX27	1221	682479	AC022834	5021	1-483
HCNCX27	1221	682479	AC022834	5022	1-478
HCNCX27	1221	682479	AC023214	5023	1-483
HCNCX27	1221	682479	AC023214	5024	1-345
HCNCT03	1222	923344	AL139155	5025	1-471
HCNCO59	1223	738889	AL133384	5026	1-841

HCNCF19	1225	668043	AC016757	5027	1-825
HCNCF19	1225	668043	AC016757	5028	1-278
HCNAZ20	1226	670031	AC022744	5029	1-543
HCNAZ20	1226	670031	AC015531	5030	1-543
HCNAZ20	1226	670031	AC009588	5031	1-543
HCNAZ20	1226	670031	AC022744	5032	1-224
HCNAZ20	1226	670031	AC015531	5033	1-224
HCNAZ20	1226	670031	AC009588	5034	1-224
HCNAT92	1228	518899	AC025883	5035	1-108 447-498 2019-2265
HCNAT92	1228	518899	AC025883	5036	1-376
HCNAT67	1229	508295	AC027678	5037	1-94 1661-1725 5796-6058 6224-6585 7182-7626
HCNAT67	1229	508295	AC022390	5038	1-192 1664-1728 5801-6062 6228-6589 7186-10078
HCNAQ26	1230	685199	AC072035	5039	1-1115
HCNAQ26	1230	685199	AC012404	5040	1-1115
HCNAP29	1231	855685	AC012320	5041	1-455
HCNAP29	1231	855685	AC004382	5042	1-455
HCNAL30	1232	522672	AC004519	5043	1-120
HCNAK11	1233	967945	AC003991	5044	1-977
HCNAA41	1234	791545	AF231129	5045	1-970
HCNAA41	1234	791545	AC026458	5046	1-1382
HCNAA41	1234	791545	AC069047	5047	1-236 552-842 1745-3603 3697-3797 3977-4311 4540-5215 5349-5754 5897-6069 6293-6847 7430-7862 8779-9218
HCNAA41	1234	791545	AC022674	5048	1-196 398-598 605-680 811-1547 1568-2200 2208-3590

					4511-5262 5305-5455 5885-5993 6125-6553
HCNAA41	1234	791545	AC026458	5049	1-191
HCNAA41	1234	791545	AC069047	5050	1-224
HCNAA41	1234	791545	AC026458	5051	1-467
HCNAA41	1234	791545	AC069047	5052	1-276 291-329 335-615
HCNAA41	1234	791545	AC022674	5053	1-225
HCLHE01	1235	914341	AC015936	5054	1-867 941-1038 1445-2109
HCLHE01	1235	914341	AC015936	5055	1-2147
HCIAC12	1237	970750	AL365321	5056	1-300 888-1011
HCIAC12	1237	970750	AL137856	5057	1-300 888-1011
HCIAC12	1237	970750	AL137856	5058	1-129
HASMC23	1238	675527	AC078779	5059	1-437
HASMC23	1238	675527	AC007879	5060	1-437
HASMC23	1238	675527	AC078779	5061	1-678
HASMC23	1238	675527	AC007879	5062	1-678
HAQNB68	1240	752573	AL355527	5063	1-732 915-1304
HAQNB68	1240	752573	AC031978	5064	1-732 915-1304
HAQNB68	1240	752573	AL355527	5065	1-195 4293-4519 5143-5283 5581-6183 6220-6565
HAQNB68	1240	752573	AL355527	5066	1-525
HAQNB68	1240	752573	AC031978	5067	1-509 787-1159 1256-1670 2179-2779 3028-3227 3307-3816 4090-4193 4926-5105 5203-5628 6078-7654 7723-8191 8290-9353 9574-9769

					13869-14095 14719-14859 15157-15759 15796-16141
HAQNB68	1240	752573	AC031978	5068	1-525
HAQMP04	1241	925685	AC013399	5069	1-745
HAQMP04	1241	925685	AC013399	5070	1-511
HAQMK53	1242	727708	AC022702	5071	1-220 2365-2620 2992-3310 3432-3987 4545-5235 5266-5325 5814-6468 6801-6965 7327-7763 7979-8172
HAQMK53	1242	727708	AC025796	5072	1-556
HAQMK53	1242	727708	AL133216	5073	1-306 1488-1890 2450-2722 3082-3400 3526-4081 4304-5314
HAQMK53	1242	727708	AC006457	5074	1-513
HAQMK53	1242	727708	AF198096	5075	1-308 1490-1896 2457-2728 2816-3407 3532-4087 4313-5008 5584-6209
HAQMK53	1242	727708	AC022702	5076	1-316
HAQMK53	1242	727708	AC025796	5077	1-592
HAQMK53	1242	727708	AC025796	5078	1-694
HAQMK53	1242	727708	AL133216	5079	1-750
HAQMK53	1242	727708	AL133216	5080	1-138 734-1117 1716-2301 2496-3003 3142-3588 5476-6185 6679-7322 7428-7952 8163-8628 9071-9154 9380-9538

					10422-10640 10673-10765 10780-10828 11018-11735 12735-13548 13651-14193 14663-14949 15056-15454 17688-18060 19315-19659
HAQMK53	1242	727708	AC006457	5081	1-319
HAQMK53	1242	727708	AF198096	5082	1-2408
HAQMK53	1242	727708	AF198096	5083	1-373
HALSD90	1244	500844	AL358788	5084	1-326
HALSD90	1244	500844	AL035703	5085	1-326
HALSD90	1244	500844	AL358788	5086	1-303
HALSD90	1244	500844	AL358788	5087	1-169
HALSD90	1244	500844	AL035703	5088	1-169
HALSD90	1244	500844	AL035703	5089	1-281
HALSD51	1245	500852	AL358785	5090	1-257 287-692 1417-1580 2345-2567 3689-4208 5913-6558 6925-7555 7993-8428 9734-10170 10340-10967 10992-11330 12284-14337
HALSD51	1245	500852	AC005678	5091	1-257 287-692 1417-1580 2345-2567 3689-4208 5913-6558 6925-7555 7993-8428 9734-10170 10340-10967 10992-11330 12284-13526
HALSD51	1245	500852	AC005678	5092	1-781
HALSD51	1245	500852	AL358785	5093	1-102
HALSD34	1246	509765	AC025648	5094	1-360
HALSD34	1246	509765	AC025062	5095	1-360

HALSD34	1246	509765	AC025648	5096	1-353
HALSD03	1247	960910	AC025389	5097	1-382
HALSD03	1247	960910	AC025389	5098	1-449
HALSD03	1247	960910	AC025389	5099	1-387 1195-2050 2234-2844
HALSC37	1248	705894	AL359926	5100	1-303
HALSC37	1248	705894	AL359175	5101	1-303
HALSC37	1248	705894	AL359926	5102	1-337
HALSC18	1249	667044	AC068037	5103	1-346
HALSC18	1249	667044	AC068037	5104	1-492
HAJRA03	1250	923504	AC025515	5105	1-988
HAJRA03	1250	923504	AC025515	5106	1-1719
H2MBY07	1252	953691	AC018881	5107	1-1603
H2MBY07	1252	953691	AC018881	5108	1-225
H2LAM15	1258	767606	AC005971	5109	1-384 1607-2194 2501-2679 2714-3008 3294-5645 5706-5867 7869-8294 8698-8815 9677-9738 10469-10894 16079-16366 18971-19267 19303-19634 22325-22853 23664-23983 24003-24401 24470-24690 25545-26062 26253-27613 29664-29801 35223-36709
H2LAM15	1258	767606	AL356460	5110	1-296 1519-2272 2413-2591 2626-2920 3206-5559 5620-5781 7784-8208 8613-8730 9592-9653 10384-10809 13353-13493

					16165-16265 18887-19122 19219-19549 22239-22666 22710-23025 23112-23564 23898-24217 24237-24635 24704-24924 25767-26284 26475-27836 30276-30380 33861-34003 35218-35346 35446-36933
H2LAM15	1258	767606	AC005971	5111	1-89
H2LAM15	1258	767606	AL356460	5112	1-383
H2CBP41	1259	923006	AC027116	5113	1-417 1542-1883 2547-2644 3234-3317 4045-4387 4561-4942 5029-5287 6230-6850 6936-7598 7713-8015 8248-8896
H2CBP41	1259	923006	AC021329	5114	1-417 1542-1883 2547-2644 3234-3317 4045-4387 4561-4942 5029-5287 6230-6850 6936-7597 7712-8014 8247-8895
H2CBP41	1259	923006	AC027116	5115	1-5853 5877-7569
H2CBP41	1259	923006	AC021329	5116	1-5853 5877-7569

[073] Table 1B summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences



(contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

**TABLE 2**

Clone ID NO:Z	Contig ID:	SEQ ID NO:X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/ Percent Identity	NT From	NT To
H2CBG54	893910	11	blastx.2	(AK000657) unnamed protein product [Homo sapiens]	dbj BAA91310.1	96%	54	593
HALSK15	501003	18	blastx.2	sodium phosphate transporter [Homo sapiens]	gb AAB53422.1	100%	15	131
HBAAE56	953244	22	HMMER 1.8	PFAM: Core histones H2A, H2B, H3 and H4	PF00125	11.56	94	159
HCNDL91	832209	50	blastx.2	transformation-related protein [Homo sapiens]	gb AAA36776.1	60% 50% 33%	341 121 142	222 86 80
HCNUA60	695786	57	HMMER 2.1.1	PFAM: Uncharacterized protein family	PF01027	24.9	132	224
HCRM69	877118	65	blastx.2	(AF151877) CGI-119 protein [Homo sapiens]	gb AAD34114.1 AF15 1877.1	100%	135	206
			HMMER 2.1.1	PFAM: N2,N2- dimethylguanosine tRNA methyltransferase	PF02005	44.3	194	292
HCRMT41	974324	66	blastx.2	(AC005546) R29425_1 [Homo sapiens]	gb AAC33150.1	96% 77% 80% 100%	194 274 58 32	292 381 120 73
			blastx.2	similar to Na+/H+ antiporter [Bacillus subtilis]	emb CABI4288.1	28%	133	486
			blastx.2	[dl 970227] Weak splice	emb CAB03422.1	29%	93	563

HCROE42	950701	72	blastx.2	needed to incorporate EST & BlastX 1 1 1 cDN (AF184344) DNA polymerase accessory subunit precursor [Homo sapiens]	gb AAD56542.1 AF18 4344_1	99% 77%	3 679	683 840
HCRPT92	931152	77	HMMER 2.1.1 blastx.2	PFAM: Cytosol aminopeptidase family (AF218811) putative cytoplasmic aminopeptidase 1	PF00883 gb AAF32328.1 AF21 8811_1	261 74%	14 5	676 727
HCRQG35	954968	80	blastx.2	unnamed protein product [unidentified]	emb CAB69195.1	81%	11	91
HDRMA28	841936	83	blastx.2	(AK002129) unnamed protein product [Homo sapiens]	dbj BAA92096.1	67%	152	280
HFLQA82	757380	89	HMMER 1.8	PFAM: C2 domain	PF00168	3.08	52	90
HFLSH67	968639	92	blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]	gb AAC08737.1	68% 67% 56% 46%	174 176 291 270	269 268 359 359
HFLSK11	964908	95	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	3.01	159	197
HFLUF43	928026	98	blastx.2	(AF090894) PRO0113 [Homo sapiens]	gb AAF24018.1 AF09 0894_1	67%	853	716
HFLVE61	539872	101	blastx.2	lambda HuHIT1-13 [Homo sapiens]	emb CAA32821.1	99% 100%	1 320	306 343

HFLVII5	921860	103	blastx.2	5-methyltetrahydrofolate-homocysteine transferase (AA 1-1200) 1	emb CAA34601.1	97%	320	9
HFVHF81	929124	111	HMMER 1.8	PFAM: Ubiquitin carboxyl-terminal hydrolases family 2	PF00442	82%	379	329
HGBAU93	625250	134	blastx.2	(AL117458) hypothetical protein [Homo sapiens]	emb CAB55936.1	36%	441	319
HGBBO62	509691	137	blastx.2	(AF192522) Niemann-Pick C3 protein; NPC3 [Homo sapiens]	gb AAF20396.1 AF192522_1	10.34	187	210
HGBDB04	961510	141	blastx.2	(AF151072) HSPC238 [Homo sapiens]	gb AAF36158.1 AF151072_1	50%	1	165
HGBDG69	578390	148	blastx.2	(AL137370) hypothetical protein [Homo sapiens]	emb CAB70714.1	55%	207	287
HGBDY59	815818	158	HMMER 2.1.1	PFAM: Calpain family cysteine protease	PF00648	100%	3	125
HGBGO22	558830	163	blastx.2	calpain [Rattus norvegicus]	dbj BAA03371.1	97%	38	256
			HMMER 1.8	PFAM: Annexins	PF00191	83%	246	338
			blastx.2	intestine-specific annexin [Homo sapiens]	emb CAA77578.1	39%	283	360
HGOCB25	506771	174	blastx.2	(AF161356) HSPC093 [Homo sapiens]	gb AAF28916.1 AF161356_1	70%	28	282
HISCN24	764837	199	blastx.2	(AK001360) unnamed	dbj BAA91648.1	86.3	9	167
						87%	176	454
						87%	3	167
						35.5	114	272
						51%	25	291
						40%	84	356
						48%	143	352
						53%	210	1
						86%	175	312

HISDO59	857479	203	blastx.2	protein product [Homo sapiens] (AF113685) PRO0974 [Homo sapiens]	gb AAF29584.1 AF113685_1	52% 58%	331 105	119 55
HLDBJ86	882365	217	blastx.2	(AF097518) liver-specific transporter [Homo sapiens]	gb AAD37091.1 AF097518_1	74% 100%	35 378	334 431
HLDCI35	831356	221	HMMER 1.8	PFAM: Helicases conserved C-terminal domain	PF00271	6.01	288	374
HLDCU27	950724	222	blastx.2	(AF209192) Apobec-1 complementation factor [Homo 1]	gb AAF34824.1 AF209192_1	94%	177	725
HLDDH01	926360	223	HMMER 2.1.1 blastx.2	PFAM: Collagen triple helix repeat (20 copies) GDQGE (5x) [Paramecium bursaria Chlorella virus 1]	PF01391 gb AAC97040.1	39.9 56% 37%	107 107 48	250 202 110
HLDDI91	790003	224	HMMER 2.1.1 blastx.2	PFAM: tRNA synthetases class II (D, K and N) (AE001123) asparaginyl-tRNA synthetase (asnS) [Borrelia burgdorferi]	PF00152 gb AAC66501.1	53.1 38%	15 3	140 323
			HMMER 1.8	PFAM: RNA recognition motif. (aka RRM, RBD, or RNP domain)	PF00076	60.16	393	590
			blastx.2	(AF209192) Apobec-1 complementation factor [Homo 1]	gb AAF34824.1 AF209192_1	100% 96% 97% 16%	2 351 244 104	244 602 348 262

HLDNJ57	733903	227	blastx.2	(AK001848) unnamed protein product [Homo sapiens]	dbj BAA91940.1	68%	61	399
HLDNU53	883158	228	blastx.2	(AF097518) liver-specific transporter [Homo sapiens]	gb AAD37091.1 AF097518_1	71%	3	182
HLDQA63	949166	229	HMMER 2.1.1	PFAM: NTR/C345C module	PF01759	34.1	144	323
			blastx.2	complement C3 protein (GPC3) precursor [Cavia porcellus]	gb AAA37038.1	35%	72	449
HLDON90	788891	232	HMMER 1.8	PFAM: Laminin B (Domain IV)	PF00052	1.99	77	100
HLDQU12	857106	234	blastx.2	(AF202889) regeneration associated protein 3 [Homo sapiens]	gb AAF25661.1 AF202889_1	100%	1	99
HLDQC62	923559	239	blastx.2	(AF091457) zinc finger protein RIN ZF [Rattus norvegicus]	gb AAD22522.1 AF091457_1	50% 51%	1302 1036	1039 941
HLDRD54	727954	243	blastx.2	(AF090944) PRO0663 [Homo sapiens]	gb AAF24056.1 AF090944_1	62%	121	240
HLDQR82	837031	248	blastx.2	(AF064255) very long-chain acyl-CoA synthetase homolog 2; VLCS-H2 [Homo sapiens]	gb AAD29444.1 AF064255_1	100% 87% 100%	325 143 3	582 340 140
HLIBJ13	910830	251	HMMER 2.1.1	PFAM: Fibrinogen beta and gamma chains, C-terminal globular domain	PF00147	153.7	72	389
			blastx.2	(AF152562) angiopoietin-	gb AAD34156.1 AF15	90%	60	422

HLICR73	837030	255	HMMER 1.8	related protein 3 [Homo sapiens] PFAM: AMP-binding enzymes	2562_1 PF00501	20.33	19	324
			blastx.2	(AF064255) very long-chain acyl-CoA synthetase homolog 2; VLCS-H2 [Homo sapiens]	gb AAD29444.1 AF064255_1	99% 100%	1 450	441 497
HLQAL33	702755	260	blastx.2	hypothetical L1 protein (third intron of gene TS) - human	pir JU0033 JU0033	38%	347	3
HLQAZ69	960046	262	blastx.2	(AF139185) myomegalin [Rattus norvegicus]	gb AAD29427.1	77%	31	201
HLQBF72	608371	263	HMMER 2.1.1 blastx.2	PFAM: HECT-domain (ubiquitin-transferase). (AF199364) E3 ubiquitin ligase SMURF1 [Homo sapiens]	PF00632 gb AAF08298.2	32.6 96%	189 189	284 284
HLQB121	529342	265	blastx.2	(AL121739) hypothetical protein [Homo sapiens]	emb CAB57329.1	97%	10	120
HLQDP11	966775	274	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	55%	53	292
HLQDY10	856755	276	blastx.2	alternatively spliced product using exon 13A [Homo sapiens]	gb AAB49034.1	75% 85%	379 459	284 439
HLQED11	966015	277	blastx.2	(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	63% 82%	21 91	86 141

HLQFO69	933385	282	HMMER 2.1.1 blastx.2	sapiens] PFAM: HECT-domain (ubiquitin-transferase). hypothetical protein 2 - human (fragment)	PF00632	87.8	245	553
HLQGN56	842004	284	blastx.2	CRP2 (cysteine-rich protein 2) [Rattus norvegicus]	pir B38919 B38919	72%	254	550
HNAAE73	922929	288	blastx.2	unknown [Homo sapiens]	dbj BAA04464.1	78% 70%	1 1	150 150
HNJBA08	955993	290	HMMER 1.8	(AF190862) ADP- ribosylation factor binding protein GGA1 [Homo sapiens]	gb AAF05707.1 AF19 0862_1	80% 51%	506 426	414 271
HNJBL71	939266	293	blastx.2	PFAM: HMG (high mobility group) box	PF00505	4.88	482	547
HNJBN94	948996	294	HMMER 2.1.1 blastx.2	(AF081497) tumor-related protein [Homo sapiens]	gb AAD55748.1 AF08 1497_1	98%	1	192
HNJCD23	961494	296	HMMER 1.8	PFAM: LBP / BPI / CETP family	PF01273	37.8	34	636
HNJEA92	955842	298	blastx.2	potential ligand-binding protein [Rattus rattus]	emb CAA43067.1	28%	103	621
HNKBB44	955843	301	blastx.2	PFAM: Protamine P1	PF00260	45.65	89	223
				unknown [Mus musculus]	gb AAB63256.1	75% 55% 60%	349 70 136	837 198 210
				unknown [Mus musculus]	gb AAB63256.1	68%	834	274



HNKBS78	955565	303	blastx.2	unknown [Mus musculus]	gb AAB63256.1	74%	700	227
HROAL51	526487	313	blastx.2	zinc finger protein [Homo sapiens]	gb AAA59469.1	77%	125	45
HROBC76	880935	317	HMMER 2.1.1	PFAM: Ammonium Transporter Family	PF00909	44%	221	150
			blastx.2	(AF081497) tumor-related protein [Homo sapiens]	gb AAD55748.1 AF081497.1	38.7	3	119
HROBQ03	867044	321	blastx.2	X-linked retinopathy protein [C-terminal, clone XEH.8c] [human, Peptide Partial, 100 aa] [Homo sapiens]	gb AAB26149.1	52% 69%	3 157	359 300
						73% 81%	276 349	353 381
HSICR69	531061	340	HMMER 1.8	PFAM: Phorbol esters / diacylglycerol binding domain	PF00130	3.1	190	213
HSICX21	531267	344	HMMER 1.8	PFAM: Zinc-binding metalloprotease domain	PF00099	3.8	307	336
HSIDW39	775139	361	HMMER 2.1.1	PFAM: Glycosyl hydrolase family 1	PF00232	134	28	372
			blastx.2	cytosolic beta-glucosidase [Cavia porcellus]	gb AAB41058.1	84%	1	363
HSIDW39	830774	1261	HMMER 2.1.1	PFAM: Glycosyl hydrolase family 1	PF00232	155.5	42	419
HSIEE78	904664	364	blastx.2	epidermal growth factor receptor kinase substrate [Homo sapiens]	gb AAA62280.1	36% 62% 35% 40%	214 1138 768 774	657 1185 869 848
HSIEO17	922867	367	HMMER	PFAM: TPR Domain	PF00515	10.76	376	417

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				[Drosophila melanogaster]				68%	143	208
HTPDV73	912947	462	HMMER 1.8	PFAM: Ras family (contains ATP/GTP binding P-loop)	PF00071			92%	58	99
			blastx.2	(AL049685) hypothetical protein [Homo sapiens]	emb CAB41256.1			91%	3	38
			blastx.2	ORF 3 [Homo sapiens]	gb AAA58464.1			75%	35	58
HTPDZ94	660751	465	blastx.2					205.32	306	740
			blastx.2	human type 3 inositol 1,4,5-trisphosphate receptor [Homo sapiens]	gb AAC50064.1			97%	312	746
HTPFQ07	869785	474	blastx.2	(AF118086) PRO1992 [Homo sapiens]	gb AAF22030.1 AF11 8094 25			53%	262	101
HTPFZ03	922755	481	blastx.2	(AL049847) hypothetical protein [Homo sapiens]	emb CAB42851.1			62%	342	271
HTPGD19	869842	482	blastx.2	PFAM: SCAN domain	PF02023			46%	93	4
HTPGW12	969522	489	HMMER 2.1.1	serum response element- binding protein SRE-ZBP - human (fragment)	pir A44391 A44391			90%	261	380
			blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]	gb AAC08737.1			73%	18	116
HTPHK06	975310	494	blastx.2	(AK000546) unnamed	dbj BAA91245.1			87%	365	535
HTPIC25	975319	499	blastx.2					92%	294	368
								117.3	4	192
								72%	4	180
								40%	226	282
								53%	228	266
								81%	288	383
								52%	300	464
								60%	383	472
								32%	28	429

HTPIE48	911422	500	HMMER 1.8	protein product [Homo sapiens] PFAM: Src homology domain 3	PF00018	3.78	2	58
			blastx.2	(AC005954) ZO-3 [Homo sapiens]	gb AAC72274.1	80%	2	313
HUFAA81	777951	501	blastx.2	unknown [Homo sapiens]	gb AAC50940.1	58%	155	358
HUFAC65	750264	502	blastx.2	(AL133640) hypothetical protein [Homo sapiens]	emb CAB63761.1	83%	3	302
HUFAP02	919805	507	blastx.2	biliverdin-IXbeta reductase I [Homo sapiens]	dbj BAA06874.1	50%	293	379
						74%	121	249
HUFAU25	678024	508	HMMER 2.1.1	PFAM: RNA polymerase beta subunit	PF00562	112.6	1	141
			blastx.2	(AK001161) unnamed protein product [Homo sapiens]	dbj BAA91527.1	79%	1	309
HUFBN27	868997	510	blastx.2	initiation factor 2 [Homo sapiens]	gb AAA67038.1	99%	81	401
HUFDB55	950430	515	HMMER 2.1.1	PFAM: SEA domain	PF01390	22.9	1485	1138
			blastx.2	(AF147790) transmembrane mucin 12 [Homo sapiens]	gb AAD55678.1 AF147790_1	84%	2133	553
						41%	2058	1708
						39%	2055	1714
HUFGH78	659722	516	blastx.2	(AL035413) dJ657E11.3 (aldo-keto reductase family 7, member A3 1)	emb CAB72322.1	87%	47	313
						69%	316	480
						100%	412	483
HUVDJ10	886207	517	blastx.2	(AF010144) neuronal thread protein AD7c-NTP	gb AAC08737.1	65%	1093	854
						66%	1077	853

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HWGQF79	882611	538	blastx.2	trypsin inhibitor (Bowman-Birk) - two-rowed barley	pir JT0235 TIBHB	44%	78	185
HWLBK80	933865	543	blastx.2	The ha3662 gene product is related to mouse glycerophosphate dehydrogenase. [Homo sapiens]	dbj BAA07648.1	46%	236	280
						95%	129	380
HWLEN08	958509	553	blastx.2	predicted using Genefinder; cDNA EST yk488a2.5 comes from this gene [Caenorhabditis elegans]	emb CAB02762.1	31%	89	538
HWLEN20	963418	554	HMMER 1.8	PFAM: Zinc finger, C3HC4 type (RING finger)	PF00097	8.49	198	233
HWLEO59	974078	555	blastx.2	(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	78%	241	101
						56%	401	231
HWLFB08	849136	560	blastx.2	ubiquitin-conjugating enzyme [Mus musculus]	emb CAA76720.1	80%	2	517
HWLFE50	830283	562	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	67%	326	12
HWLFP37	708985	571	blastx.2	(AF090942) PRO0657 [Homo sapiens]	gb AAF24054.1 AF090942.1	65%	150	305
						54%	95	166
HWLHP05	931087	589	blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]	gb AAC08737.1	47%	418	215
						67%	417	319
						78%	305	249
						61%	417	319
						84%	59	3

HWLHR93	952387	590	HMMER 1.8	PFAM: Zinc finger, CCHC class	PF00098	48%	326	228
HWLHT06	934217	591	blastx.2	(AK000301) unnamed protein product [Homo sapiens]	dbj BAA91067.1	80%	47	3
HWLIH21	917551	595	blastx.2	(AK000134) unnamed protein product [Homo sapiens]	dbj BAA90965.1	52%	417	349
HWLIL65	747440	596	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	45%	412	317
HWLJC30	830232	603	blastx.2	(AK000258) unnamed protein product [Homo sapiens]	dbj BAA91037.1	37%	326	240
HWLJL46	830226	607	blastx.2	(AF090931) PRO0483 [Homo sapiens]	gb AAF24046.1 AF09 0931 1	62%	95	421
HWLJN54	729051	608	blastx.2	(AK000400) unnamed protein product [Homo sapiens]	dbj BAA91140.1	100%	328	441
HWLJR77	883207	611	HMMER 2.1.1	PFAM: Jacalin-like lectin domain	PF01419	59%	138	13
			blastx.2	(AC002301) Homolog of rat Zymogen granule	gb AAC08708.1	34%	140	472
						34%	1	138
						55.5	271	552
						73%	166	657

HWLKC87	956205	614	HMMER 1.8	membrane protein [Homo sapiens] PFAM: UDP-glucuronosyl and UDP-glucosyl transferases	PF00201	47.54	5	133
			blastx.2	UDP-glucuronosyltransferase isoform [Homo sapiens]	gb AAD14400.1 S824_85_1	58%	5	121
HWLKW04	969141	620	HMMER 2.1.1	PFAM: Ribosomal protein S27	PF01667	107.7	176	310
			blastx.2	(AF070668) 40S ribosomal protein S27 isoform [Homo sapiens]	gb AAD20974.1	82% 80%	95 301	322 345
HWLLB11	954849	623	HMMER 1.8	PFAM: Cytochrome P450	PF00067	159.13	75	506
			blastx.2	(AF091117) cytochrome P450 [Orconectes limosus]	gb AAF09264.1 AF091117_1	40% 53%	78 1	509 90
HWLNX76	887583	631	blastx.2	(AF126484) CARD4 [Homo sapiens]	gb AAD29125.1 AF126484_1	73% 93% 35% 31% 33% 32% 81%	3 301 3 3 3 6 269	371 393 278 281 260 272 301
HWMAD05	931076	642	blastx.2	galactosylceramide-like protein, GCP - human	pir JC5238 JC5238	68%	144	22
HWME65	969190	645	HMMER 2.1.1	PFAM: Matrixin	PF00413	45.6	17	109



			blastx.2	(AB000719) hatching enzyme [Hemicentrotus pulcherrimus]	dbj BAA19171.1	51%	2	304
HWMEU56	922375	646	blastx.2	(AB012223) ORF2 [Canis familiaris]	dbj BAA25253.1	63% 53%	59 380	196 424
HWMFA28	965354	647	blastx.2	(AE001886) hypothetical protein [Deinococcus radiodurans]	gb AAF09840.1 AE001886_6	52% 50%	178 47	47 6
HWMFG32	883180	649	blastx.2	(AK002129) unnamed protein product [Homo sapiens]	dbj BAA92096.1	75%	136	5
HWMGL13	947969	653	blastx.2	laminin alpha 5 chain [Mus musculus]	gb AAC53430.1	77% 62%	3 376	371 423
HWMHG26	957665	655	blastx.2	(AL110233) hypothetical protein [Homo sapiens]	emb CAB53686.1	71% 78%	131 42	36 1
HWMHX12	914007	658	blastx.2	(AB008185) ganglioside sialidase [Homo sapiens]	dbj BAA82611.1	64% 40% 33%	15 278 572	275 619 730
HWMJB68	914031	662	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	62%	395	63
HWMKI01	913841	664	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	67%	575	372
HWMKI10	961616	665	blastx.2	(AF155219) MAB21L2 [Homo sapiens]	gb AAD40248.1 AF155219_1	100%	2	286
HWMLG23	961110	666	blastx.2	(AF151802) CGI-44 protein [Homo sapiens]	gb AAD34039.1 AF151802_1	100%	144	242

HWNCY59	927487	675	blastx.2	(AF090942) PRO0657 [Homo sapiens]	gb AAF24054.1 AF09 0942_1	80%	210	133
HWNGN09	961602	680	HMMER 1.8	PFAM: Ribosomal protein S10	PF00338	66%	238	203
			blastx.2	(AL132880) predicted using Genefinder; preliminary prediction 1	emb CAB60869.1	52.21	82	246
HXOAI14	974075	682	blastx.2	monoclonal antibody variable region heavy chain [Mus musculus]	emb CAA01970.1	57% 75%	73 29	246 85
HWNCN05	928791	686	blastx.2	(AF140675) zinc metalloprotease ADAMTS7 [Homo sapiens]	gb AAD56358.1 AF14 0675_1	39%	185	721
HWNAL06	933591	689	blastx.2	putative ribosomal protein (AA 1-184) [Homo sapiens]	emb CAA37793.1	73%	308	421
HWLPN12	969572	701	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	62% 64%	458 241	249 191
			HMMER 2.1.1	PFAM: KRAB box	PF01352	125.8	87	254
HWLOB68	908500	703	blastx.2	(A1245586) KRAB protein domain [Homo sapiens]	emb CAB52478.1	100%	93	281
			blastx.2	(AF106037) adipocyte- derived leucine aminopeptidase [Homo sapiens]	gb AAF07395.1 AF10 6037_1	96% 88%	586 650	317 576

HWLLZ91	887157	707	blastx.2	(AL022322) bK228A9.2 (novel protein similar to FAS-ligand 1 substrate) [Homo sapiens]	emb CAB62940.1	98%	143	463
HWLKT19	974292	709	blastx.2	B-cell growth factor [Homo sapiens]	gb AAB02649.1	65%	367	480
HWLKQ11	965390	710	blastx.2	(AK000928) unnamed protein product [Homo sapiens]	dbj BAA91431.1	82%	109	8
HWLKJ18	930414	711	blastx.2	(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	53% 85%	77 213	211 275
HWLJW12	969556	713	blastx.2	(AL117639) hypothetical protein [Homo sapiens]	emb CAB56027.1	96%	408	488
HWLHH62	876225	725	blastx.2	(AF115384) LR8 [Homo sapiens]	gb AAD23440.1 AF11 5384 1	100%	4	108
HWLHD19	887203	726	blastx.2	(AF071787) melastatin 1 [Homo sapiens]	gb AAC80000.1	43%	84	629
HWLGV14	967914	727	blastx.2	(AF115384) LR8 [Homo sapiens]	gb AAD23440.1 AF11 5384 1	95%	169	384
HWLFY91	789569	729	blastx.2	(AF084256) beta glucuronidase isoform d [Homo sapiens]	gb AAD17791.1	67% 63%	246 143	145 111
HWLEM80	886651	738	blastx.2	PC6B [Mus musculus]	dbj BAA04507.1	57% 34% 36% 35% 32% 33%	87 93 117 87 90 87	767 539 539 488 548 512

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HWLBN90	787355	752	HMMER 1.8	sapiens]	PF00505	5.11	440	529
			blastx.2	PFAM: HMG (high mobility group) box (AF155115) NY-REN-58 antigen [Homo sapiens]	gb AAD42881.1 AF15 5115_1	100% 100%	419 385	610 417
HWLBL75	766877	753	blastx.2	(AF060862) unknown [Homo sapiens]	gb AAC15461.1	95%	3	137
HWLBI01	919168	754	blastx.2	(AF053356) ORF3, splicevariantc [Homo sapiens]	gb AAC78797.1	94% 100%	107 52	214 72
HWCAD06	886808	763	blastx.2	(AK001122) unnamed protein product [Homo sapiens]	dbj BAA91512.1	86%	335	529
HVASJ79	951617	765	blastx.2	(AF007871) torsinA [Homo sapiens]	gb AAC51732.1	51% 39%	60 888	545 1076
HUTSF11	966029	770	HMMER 1.8	PFAM: Eukaryotic protein kinase domain	PF00069	27.74	3	104
HUTAF08	958353	771	blastx.2	ORF1; MER37; putative transposase similar to pogo element [Homo sapiens]	gb AAB61714.1	65% 66%	390 478	295 386
HUFGC48	950707	772	blastx.2	(AC004988) supported by EST AA458691 (NID:g2183598) and Genscan [Homo sapiens]	gb AAD26979.1 AC00 4988_1	96% 90%	147 287	302 316
HUFFW06	934895	773	blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]	gb AAC08737.1	43% 48%	508 343	329 251
HUFDO11	966407	775	blastx.2	(AK000385) unnamed	dbj BAA91131.1	57%	400	155

				protein product [Homo sapiens]			69%	173	135
HUFDN22	783765	776	blastx.2	(AF071173) Herc2 [Mus musculus]	gb AAD08658.1		84%	164	436
HUFCI80	773161	781	blastx.2	(AF151906) CGI-148 protein [Homo sapiens]	gb AAD34143.1 AF151906.1		98%	522	821
HUFBP22	582067	782	blastx.2	telomerase-associated protein TP-1 [Homo sapiens]	gb AAC51107.1		100%	371	520
HUFBD16	661856	783	blastx.2	transformation-related protein [Homo sapiens]	gb AAA36776.1		54%	378	220
HUFAJ16	621443	787	blastx.2	alternatively spliced product using exon 13A [Homo sapiens]	gb AAB49034.1		55%	461	384
HTPFF82	869864	792	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF118094.21		50%	2	226
HTPBU35	530440	805	blastx.2	(AF109377) ldlBp [Mus musculus]	gb AAD13780.1		48%	8	364
							78%	64	189
							88%	3	53
HTPAP93	791415	808	blastx.2	(AK001374) unnamed protein product [Homo sapiens]	dbj BAA91657.1		96%	33	218
HTPAI20	937644	810	blastx.2	(AK000305) unnamed protein product [Homo sapiens]	dbj BAA91071.1		98%	2	418
HSPAB58	736098	822	HMMER 1.8	PFAM: Zinc-binding metalloprotease domain	PF00099		4.6	39	86
HSODZ07	955932	824	HMMER	PFAM: RNA recognition	PF00076		14.64	317	388

				1.8	motif. (aka RRM, RBD, or RNP domain)					
HSOBE61	908598	842		blastx.2	(AK000867) unnamed protein product [Homo sapiens]	dbj BAA91401.1	53%	311	496	
				HMMER 1.8	PFAM: Zinc finger, C2H2 type	PF000096	11.74	226	288	
				blastx.2	zinc finger protein [Homo sapiens]	emb CAA55532.1	62%	1	300	
							50%	28	381	
							58%	13	300	
HSOAV11	967590	847					59%	16	300	
							52%	73	381	
							51%	13	300	
							67%	356	493	
							63%	356	493	
							63%	356	493	
							54%	356	493	
							67%	356	475	
							56%	356	493	
							56%	347	490	
HSIGI94	793624	857		blastx.2	(AK001374) unnamed protein product [Homo sapiens]	dbj BAA91657.1	100%	372	473	
				HMMER 1.8	PFAM: Phorbol esters / diacylglycerol binding domain	PF00130	3.15	207	239	
HSIGG54	887545	858		blastx.2	vasopressin receptor	gb AAA03623.1	53%	78	311	

HSIFR52	726370	867	blastx.2	[Rattus norvegicus] (AK001040) unnamed protein product [Homo sapiens]	dbj BAA91477.1	100%	3	251
HSIFK84	782810	869	blastx.2	(AF050078) growth arrest specific 11 [Homo sapiens]	gb AAC69518.1	58% 43% 68%	331 305 77	498 520 163
HSIDZ18	666892	875	blastx.2	(AK000627) unnamed protein product [Homo sapiens]	dbj BAA91294.1	88% 92%	36 1	296 39
HSICQ22	675004	886	blastx.2	(AK001659) unnamed protein product [Homo sapiens]	dbj BAA91818.1	100%	292	152
HSICP86	785733	887	HMMER 2.1.1 blastx.2	PFAM: MAM domain. MAM domain protein [Xenopus laevis]	PF00629 gb AAC59868.1	48.4% 77%	133 64	318 318
HSIBB22	518673	889	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	64% 62%	186 259	43 188
HSIAL16	496026	891	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF11 8094_21	75% 72% 65% 73%	638 384 478 502	492 286 374 458
HSGAA12	971541	899	blastx.2	p40 [Homo sapiens]	gb AAC51270.1	40% 26%	205 75	432 194
HRTAN72	766328	903	blastx.2	unknown [Homo sapiens]	gb AAB50206.1	67% 34%	150 28	260 114



HRTAE57	871385	907	blastx.2	(AF201947) MEK binding partner 1 [Homo sapiens]	gb AAF17239.1 AF201947_1	87%	158	388
HRODU82	779482	913	blastx.2	(AB017551) 16G2 [Homo sapiens]	dbj BAA78341.1	87% 93% 87%	5 376 312	334 522 383
HRODD02	918978	915	blastx.2	(AF205935) MGA protein [Mus musculus]	gb AAF24761.1	59% 71% 38%	27 158 3	188 268 80
HROAZ07	973603	931	HMMER 1.8 blastx.2	PFAM: Flagella basal body rod proteins Molybdopterin-converting factor 16k chain [Escherichia coli]	PF00460 dbj BAA35443.1	33.9% 70%	5 113	97 469
HROAL96	867080	938	blastx.2	unknown [Homo sapiens]	gb AAB50206.1	71%	662	456
HNSMC05	840216	950	blastx.2	(AL110249) hypothetical protein [Homo sapiens]	emb CAB53697.1	79%	417	590
HNSAA51	971484	951	HMMER 2.1.1 blastx.2	PFAM: Glycosyl hydrolases family 18 (AB025008) novel member of chitinase family [Homo sapiens]	PF00704 dbj BAA86980.1	94.6% 83%	76 55	279 612
HNKAZ51	947067	953	HMMER 1.8 blastx.2	PFAM: Trypsin (AF064819) serine protease DESC1 [Homo sapiens]	PF00089 gb AAF04328.1 AF064819_1	124.58% 42% 35% 46%	259 100 677 603	594 603 832 686
HNAAE09	888913	961	blastx.2	unnamed protein product [unidentified]	emb CAB69195.1	100%	2	70

HMZME85	861084	962	blastx.2	(AF089744) xenotropic and polytropic murine leukemia virus receptor X3 [Homo sapiens]	gb AAD10196.1	96% 83%	2 442	418 672
HMZAC09	625188	966	blastx.2	(AB026833) chloride channel protein [Homo sapiens]	dbj BAA77810.1	84% 48%	288 637	596 717
HLQIF28	856619	970	HMMER 2.1.1 blastx.2	PFAM: FMN-dependent dehydrogenase (AB024079) a liver-specific gene similar to the plant glycolate oxidase [Homo sapiens]	PF01070 dbj BAA82872.1	102.6 79%	67 25	267 354
HLQHD03	856624	971	blastx.2	(AF090930) PRO0478 [Homo sapiens]	gb AAF24045.1 AF090930 1	76%	127	240
HLQGP25	893692	974	blastx.2	(AK000928) unnamed protein product [Homo sapiens]	dbj BAA91431.1	74%	414	506
HLQFQ08	961154	978	blastx.2	(AL021474) similar to BPTI/KUNITZ inhibitor domain; cDNA EST 1 1 1	emb CAA16311.1	61% 35% 40%	421 318 497	329 124 417
HLQED04	969543	984	blastx.2	(AC003034) Homolog of rat kidney-specific (KS) gene [Homo sapiens]	gb AAC23497.1	63%	275	96
HLQDV62	743401	985	blastx.2	(AF072934) translational release factor 1 [Homo sapiens]	gb AAD12759.1	73%	2	136
HLQDJ01	916193	996	blastx.2	(AF090942) PRO0657 [Homo sapiens]	gb AAF24054.1 AF090942 1	72%	6	137

HLQDE32	707639	1000	HMMER 2.1.1	PFAM: UBA domain	PF00627	48	471	578
HLQDB69	934462	1002	HMMER 2.1.1	PFAM: Calponin homology (CH) domain	PF00307	23.2	108	350
			blastx.2	(AL137527) hypothetical protein [Homo sapiens]	emb CAB70791.1	80%	12	476
HLQCY79	774827	1005	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF11 8094_21	56% 66%	72 38	167 82
HLQCI96	823602	1011	blastx.2	(AF117234) flotillin [Homo sapiens]	gb AAF17215.1 AF11 7234_1	58% 47% 56% 77%	78 3 353 388	344 305 448 414
HLPBA84	912828	1021	blastx.2	(AK000241) unnamed protein product [Homo sapiens]	dbj BAA91028.1	73% 36%	21 412	143 477
HLDOS76	770016	1042	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	68%	461	270
HLDOK25	678063	1044	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF11 8094_21	58% 66%	542 439	426 368
HLDOD83	724046	1046	blastx.2	(AF169017) forminotransferase cyclodeaminase [Homo sapiens]	gb AAF15558.1 AF16 9017_1	98% 88% 100%	625 309 662	296 232 633
HLDOC67	689240	1047	blastx.2	(AF182510) ECSIT [Mus musculus]	gb AAF01219.1 AF18 2510_1	64% 83% 45%	129 2 326	320 145 451
HLDNL57	963552	1051	blastx.2	(AK001778) unnamed	dbj BAA91904.1	100%	115	267

					protein product [Homo sapiens]			96%	42	119
HLDBV65	764915	1058	HMMER 2.1.1		PFAM: POLO box duplicated region.	PF00659		93%	2	49
			blastx.2		(AF059617) serum-inducible kinase [Homo sapiens]	gb AAC14573.1		88.3	214	378
								98%	208	402
								100%	3	83
HLDBN55	731734	1060	blastx.2		(AB028021) hepatocyte nuclear factor-3 beta [Homo sapiens]	dbj BAA78106.1		100%	45	221
HLDBN03	924100	1062	blastx.2		(AK001542) unnamed protein product [Homo sapiens]	dbj BAA91748.1		100%	3	362
								81%	413	694
								100%	364	411
HLDBE09	625554	1064	blastx.2		(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1		73%	424	290
								65%	291	223
								100%	221	180
HLDBD02	920039	1066	blastx.2		(AF113685) PRO0974 [Homo sapiens]	gb AAF29584.1 AF113685_1		52%	2	247
HLDBB21	713680	1068	HMMER 1.8		PFAM: Elongation factor Tu family (contains ATP/GTP binding P-loop)	PF00009		44.67	2	166
			blastx.2		mitochondrial elongation factor Tu [Homo sapiens]	emb CAA59169.1		96%	152	376
								98%	2	166
HLDAV38	709140	1071	blastx.2		(AF118086) PRO1992 [Homo sapiens]	gb AAF22030.1 AF118094_25		78%	8	106
HLDAK33	857107	1075	blastx.2		(AF072441) calcineurin binding protein cabin 1 [Homo sapiens]	gb AAD40846.1 AF072441_1		98%	445	2

HISEI01	915375	1081	blastx.2	(AK000284) unnamed protein product [Homo sapiens]	dbj BAA91053.1	100% 83%	131 246	244 281
HISEF78	841308	1082	blastx.2	(AL049996) hypothetical protein [Homo sapiens]	emb CAB43230.1	56% 58% 75%	73 170 345	744 388 476
HISDW49	928682	1083	HMMER 2.1.1	PFAM: Monooxygenase	PF01360	83.7	517	269
HISCQ82	975205	1087	blastx.2	(AF132944) CGI-10 protein [Homo sapiens]	gb AAD27719.1 AF13 2944_1	98%	991	149
HISCF31	950628	1093	blastx.2	unknown protein [Homo sapiens]	gb AAA88036.1	46%	469	320
HISBW78	840252	1095	blastx.2	(AF159423) cysteine-rich hydrophobic 2 CHIC2 [Homo sapiens]	gb AAD55981.1 AF15 9423_1	73%	534	205
HISAB77	772155	1121	blastx.2	Pro-Pol-dUTPase polypeptide [Mus musculus]	emb CAA73251.1	45%	1	345
HGODA23	675097	1131	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	70% 68%	255 58	61 2
HGBHM18	854310	1137	blastx.2	(AK000844) unnamed protein product [Homo sapiens]	dbj BAA91396.1	66%	151	2
HGBHK55	713512	1138	blastx.2	(AF095446) syndesmos [Gallus gallus]	gb AAF29566.1 AF09 5446_1	64% 94%	142 323	216 373
				(AF000145) germinal center kinase related	gb AAC15472.1	100%	314	400

					protein kinase [Homo sapiens]							
HGBHG78	942445	1139	blastx.2		(AC024214) contains similarity to Pfam families PF01391 1 1 1	gb AAF36081.1	32%	127	483			
HGBHD89	493910	1142	blastx.2		(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	61%	46	381			
HGBHB27	950174	1144	blastx.2		(AF114494) putative tyrosine phosphatase [Homo sapiens]	gb AAF21976.1 AF114494_1	98%	858	97			
HGBFP63	745487	1151	blastx.2		cytoplasmic dynein heavy chain [Rattus norvegicus]	dbj BAA02996.1	98%	1	276			
HGBDU06	960558	1155	blastx.2		(AJ006529) putative phosphatase [Gallus gallus]	emb CAA07090.1	93%	279	425			
HFVKC87	886358	1169	blastx.2		IDN4-GGTR14 PROTEIN.	sp Q9Y6Y5 Q9Y6Y5	100%	1	87			
HFVIC30	881306	1175	blastx.2		(AF097518) liver-specific transporter [Homo sapiens]	gb AAD37091.1 AF097518_1	76%	6	290			
HFLVG70	757521	1183	blastx.2		(AL050294) hypothetical protein [Homo sapiens]	emb CAB43393.1	75%	329	424			
HFLQI68	753216	1187	HMMER 1.8		PFAM: Zinc finger, C2H2 type	PF00096	84%	289	363			
HFLQJ38	709034	1188	blastx.2		(AK000324) unnamed protein product [Homo sapiens]	dbj BAA91086.1	64%	87	161			
							80%	322	381			
							50%	13	75			
							33%	4	57			
							4.86	90	158			
							53%	3	299			
							69%	196	342			

HDDAF49	911314	1193	HMMER 1.8	sapiens] PFAM: Zinc-binding metalloprotease domain	PF00099	5.07	144	173
			blastx.2	(AL133047) hypothetical protein [Homo sapiens]	emb CAB61374.1	52%	9	269
HCYBO59	520114	1198	blastx.2	(AF006514) CHD2 [Homo sapiens]	gb AAB87382.1	65% 69%	101 349	361 387
HCROA43	948286	1203	HMMER 2.1.1	PFAM: von Willebrand factor type C domain	PF00093	83.7	181	351
			blastx.2	(AF168680) cysteine-rich repeat-containing protein 1	gb AAF34410.1 AF16 8680_1	34% 32% 26% 28% 36%	37 28 115 64 7	405 357 714 648 189
HCRND06	934631	1205	blastx.2	ZZ:beta-Gal' IgG-binding fusion protein [unidentified cloning 1	gb AAB00807.1	73%	477	599
HCQDE22	949991	1208	blastx.2	(AF072816) ABC-type transporter MRP3 [Rattus norvegicus]	gb AAC25416.1	48% 36% 70% 29%	401 221 685 88	694 403 744 249
HCNAY45	716992	1227	blastx.2	hypothetical protein Tigger 2 - human transposon MER37 1	pir S72489 S72489	85%	602	477
HCNAT67	508295	1229	blastx.2	(AF161356) HSPC093 [Homo sapiens]	gb AAF28916.1 AF16 1356_1	73% 48%	206 90	274 218
HALSD90	500844	1244	blastx.2	(AF003535) ORF2-like protein [Homo sapiens]	gb AAD04635.1	47% 55%	231 340	10 233

HALSC18	667044	1249	blastx.2	(AF090942) PRO0657 [Homo sapiens]	gb AAF24054.1 AF090942_1	61%	108	320
H2MBH48	908926	1255	HMMER 2.1.1	PFAM: Zinc finger, C2H2 type	PF00096	59.4	268	336
			blastx.2	(AF192913) zinc finger protein ZNF180 [Homo sapiens]	gb AAF07950.1 AF192913_1	47%	55	498
						50%	55	453
						44%	34	498
						44%	58	498
						47%	55	462
						47%	58	453
						43%	58	501
						50%	103	453
						47%	58	444
						41%	133	498
						45%	58	363
						30%	43	498
H2MBE37	597070	1256	blastx.2	IDN4-GGTR14 PROTEIN.	sp Q9Y6Y5 Q9Y6Y5	87%	1	96
H2MBA41	711567	1257	HMMER 1.8	PFAM: TPR Domain	PF00515	12.31	64	108
			blastx.2	(AF075050) similar to (AJ223828) small glutamine-rich tetrapeptide (SGT) [Homo sapiens]	gb AAC28459.1	87%	109	432



[074] Table 2 further characterizes certain encoded polypeptides of the invention, by providing the results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO:", corresponding to a cDNA clone disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the row was determined. The fifth column provides a description of PFam/NR hits having significant matches identified by each analysis. Column six provides the accession number of the PFam/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFam"), as described below.

[075] The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis). Each of the polynucleotides shown in Table 1A, column 3 (e.g., SEQ ID NO:X or the 'Query' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Query sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish et al., Nat. Genet. 3:266-272 (1993)). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than  $1.0e-07$ , and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7.

The percent identity is determined by dividing the number of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

[076] The PFam database, PFam version 5.2, (Sonnhammer et al., Nucl. Acids Res., 26:320-322, (1998)) consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden Markov Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., R. Durbin et al., *Biological sequence analysis: probabilistic models of proteins and nucleic acids*, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1A) to each of the HMMs derived from PFam version 5.2. A HMM derived from PFam version 5.2 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFam family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFam hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO:X which encode the polypeptide sequence which shows a significant match to a PFam protein family.

[077] As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFam/NR database as disclosed in the fifth column of Table 2. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

[078] The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in Clone ID NO:Z. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table 1A.

[079] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[080] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA Clone ID NO:Z (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, 6 and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

[081] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

*RACE Protocol For Recovery of Full-Length Genes*

[082] Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l. Acad. Sci. USA, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation. The following briefly describes a modification of this original 5' RACE procedure. Poly A<sup>+</sup> or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, Sall and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or Sall, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar

methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

[083] Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., *Nucleic Acids Res.*, 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

[084] An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

#### *RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes*

[085] Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., *Nucleic Acids Res.*, 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is

used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase, if used, is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the digestive system antigen of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant digestive system antigen.

[086] The present invention also relates to vectors or plasmids, which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, 6 and 7) is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown, for example, in Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described, for example, in Table 1A (Clone ID NO:Z). A clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore,

although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCC Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A or 2 by procedures hereinafter further described, and others apparent to those skilled in the art.

[087] Also provided in Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

[088] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

[089] Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59- (1993). Vector lacmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

[090] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (Clone ID NO:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

[091] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of digestive system associated genes corresponding to SEQ ID NO:X or the complement thereof, polypeptides encoded by SEQ ID NO:X or the complement thereof, and/or the cDNA contained in Clone ID NO:Z, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

[092] The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[093] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[094] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).



Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the digestive system polypeptides of the present invention in methods which are well known in the art.

[095] The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in Clone ID NO:Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in Clone ID NO:Z and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, a nucleic acid sequence encoding a polypeptide encoded by the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in Clone ID NO:Z.

[096] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1B column 6, or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table

1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[097] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B,

column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[098] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0999] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1B column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0100] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other

polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0101] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID NO:Z. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0102] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same row of column 6 of Table 1B. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0103] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0104] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0105] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0106] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other

polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

[0107] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0108] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same Clone ID NO:Z (see Table 1B, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0109] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent

hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0110] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0111] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. Accordingly, for each contig sequence (SEQ ID NO:X) listed in the third column of Table 1A, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides



comprising a nucleotide sequence described by the general formula of a-b, where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

**TABLE 3**

Clone ID NO: Z	SEQ ID NO: X	Contig ID:	EST Disclaimer Range of a Range of b	Accession #'s
H2CBG54	11	893910	1 - 629 15 - 643	AA088716, AA307227, C16984, C18376, N39732, AA883812, and AB031478.
H2MBV93	12	686344	1 - 482 15 - 496	AA315111.
HALSC22	13	503082	1 - 323 15 - 337	AA358037, AI684486, W19887, AA284345, and AA385699.
HALSE71	14	509638	1 - 133 15 - 147	
HALSG01	15	500834	1 - 330 15 - 344	
HALSH86	16	501004	1 - 191 15 - 205	
HALSJ15	17	501008	1 - 262 15 - 276	AI432133.
HALSK15	18	501003	1 - 626 15 - 640	AA344831, R06460, H60423, AR036570, U90544, AR036572, and U91328.
HALSL45	19	723542	1 - 467 15 - 481	N51075, AA568306, N51117, AA708939, N51516, and AA570794.
HALSN27	20	509759	1 - 306 15 - 320	
HALSN49	21	971590	1 - 205 15 - 219	
HBAAE56	22	953244	1 - 153 15 - 167	AL119457, AL119399, AL042544, AL119324, AI874228, AL048427, AL043168, AL119511, AL079794, AL042382, AL134999, AI538564, AL043152, AI280670, AI872074, AI608805, AI571000, AI745485, AW080856, AI433037, AI251830, AI799199, AI349598, AW269097, AI309443, AI564602, AL049053, AW079736, AI590997, AA761557, AI537735, AI474137, AI921057, AW104196, AI634221, AW089572, AA603709, AI828714, AI890057, AI863477, AI690946, AI890806, AA641818, AI343091, AI598061, AI364788, AI434741, AL045500, AI636719, AI680457, AI866741, AW071362, AW301300, AI348917, AI343059, AW161202, AI433037, AI270561, AI872051, AI349933, AW192375, AI307543, AI307210, AA715307, AW129271, AA809974, AI340659, AI345253, AI799195, AI345005, AI311892, AI307736, AA748353, AI349266, AW051059, AI798258, AI636581, AW059713, AA494167, AI800152, AL045421, AW168402, AI689420, AA830821, AI433157,

AI648567, AI554821, AI434274, AW151136, AW151979, AI590635, AI539771, AW002174, AW168723, AI432644, AI636619, AA468418, AI537677, AI494201, AW263804, AW083804, AI824444, AI890907, AI038864, AI500659, AI866465, AI815232, AI345315, AI801325, AI500523, AI886022, AI538850, AW082600, AI887775, AI582932, AI284517, AI923989, AI872423, AI590043, AI500706, AI610667, AI568060, AI445237, AI491776, AI536910, AW151138, AW088144, AI521560, AI889189, AI866002, AI500662, AI539800, AW172723, AI582912, AI284509, AI889168, AI440263, AI538885, AI886594, AI866573, AI633493, AI434256, AI273179, AI866469, AI636788, AI805769, AI434242, AI888661, AW191003, AI284513, AI500714, AI888118, AW131989, AI889147, AI355779, AI436429, AI859991, AI623736, AI889147, AI285439, AI371228, AI581033, AI440252, AI491710, AI047422, AI783861, AI866786, AI610557, AI860003, AI242736, AI589267, AI828574, AI761489, AI863256, AI874351, AI887499, AI923046, AI046052, AI567978, AI539781, AI539707, AI866585, AI048375, AI127461, AI885949, AW089557, AI559957, AI521571, AI249877, AI469775, AW081255, AI932949, AI282355, AI037030, AI119791, AW084056, AI917963, AI866581, AI040241, AI867042, AI590764, AW059828, AI815150, AA806719, AI037582, AI345111, AI037602, AI446373, AW193467, AI047387, AW268261, AW162194, AI473451, AI752007, AW084097, AI922365, AI473528, AI738852, AI805638, AI046618, AI366549, AI225047, AI038761, AI046595, AI349276, AI345677, AI335363, AI046463, AI046466, AI540606, AI446605, AI348897, AI345224, AI036274, AW191844, AI264741, AI349246, AI048323, AA579232, AI863191, AI671642, AI589428, W60514, AI570384, AA493647, AL037454, AI048340, AI310925, AI334930, AI038605, U77594, Y11587, U49434, AF110329, AI8777, D55641, AF047716, S77771, I48978, L10353, A08916, AL080060, I89947,

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HBAAF58	23	861603	1 - 411	15 - 425		
HCLHD88	24	929223	1 - 458	15 - 472	AL109839.	
HCNAC10	25	968738	1 - 269	15 - 283	AA327049, AA327048, AI821708, and AA584428.	
HCNAG07	26	954493	1 - 317	15 - 331	AA327124, and AA326960.	
HCNAK56	27	832249	1 - 243	15 - 257	AA327304.	
HCNAL66	28	832247	1 - 654	15 - 668	AI307359, AI034463, AI831739, AI335097, AA970710, AI003652, AI221942, N52528, AA854422, AI022540, AI301777, and U10994.	
HCNAN69	29	655816	1 - 304	15 - 318	AA327349, and AA327350.	
HCNAO20	30	832251	1 - 321	15 - 335	AA327061, R11625, and H93223.	
HCNAR21	31	948746	1 - 418	15 - 432	AA327375, and AA327513.	
HCNAX26	32	832250	1 - 248	15 - 262		
HCNCF73	33	762056	1 - 306	15 - 320	AI027472.	
HCNCH64	34	922009	1 - 299	15 - 313		
HCNCN84	35	766990	1 - 258	15 - 272		
HCNCQ46	36	832349	1 - 171	15 - 185		
HCNCQ79	37	832242	1 - 503	15 - 517	AA327038.	
HCNCQ81	38	887923	1 - 119	15 - 133		
HCNCU02	39	918993	1 - 251	15 - 265	F24030, and AC005971.	
HCNCU83	40	731739	1 - 499	15 - 513	AC004765.	
HCNCV19	41	832221	1 - 438	15 - 452	AA327209, and AC008372.	
HCNCY39	42	960373	1 - 298	15 - 312	AC004874.	
HCNDB53	43	832225	1 - 389	15 - 403	AA327062.	
HCNDD83	44	832230	1 - 259	15 - 273		
HCNDF20	45	669111	1 - 245	15 - 259		
HCNDG69	46	666726	1 - 387	15 - 401	D31061, R70450, and AL080250.	
HCNDH18	47	832215	1 - 269	15 - 283	AA327490.	

HCNDI01	48	832213	1 - 324	15 - 338	AA327395.
HCNDK62	49	742883	1 - 406	15 - 420	AA345691.
HCNDL91	50	832209	1 - 332	15 - 346	AA715255, AA715267, AL048925, AC002091, AC007308, AC002470, AL080243, AL139054, AP000346, AC002544, AL022722, AC003695, Z95152, AC007193, and Y07848.
HCNDN43	51	832212	1 - 286	15 - 300	
HCNDQ50	52	723976	1 - 379	15 - 393	
HCNDV42	53	927262	1 - 417	15 - 431	
HCNSM15	54	914484	1 - 397	15 - 411	
HCNSP37	55	655829	1 - 253	15 - 267	H95975, AW392026, AW391990, N31464, and AW365086.
HCNSQ03	56	832200	1 - 357	15 - 371	
HCNUA60	57	695786	1 - 250	15 - 264	AC005046. R24685, AA469072, AA935534, T50287, AA887381, AI538082, AA809455, AA532665, AA970480, AA833673, AA809439, AA018103, AI419770, AA059058, AA838000, AI654089, AI784506, AA904689, AA575958, AI083552, AI806808, AI261311, AI580662, AA887119, AI268976, AA971980, AI361312, N58823, AA088862, N40196, AA019739, AA906201, AW189948, AW009062, AI188971, AI751250, AI186697, AA610052, AI310126, AI684587, AI189791, AW440198, AW264561, H86494, AI800634, AA886637, T47520, AI971218, H86061, AF113127, AF151877, AL117550, and AF161526.
HCNUA84	58	522523	1 - 339	15 - 353	AL035693.
HCQAK31	59	915563	1 - 1178	15 - 1192	AI361034, AW303442, AA587368, AI791894, AI422741, AI026698, AI693765, AI285296, AA576712, AA970211, AI692362, AI355916, AW009839, AI681730, AW376900, AW377010, AA887622, AW376964, AW376895, AA554138, AW377005, AI318042, AW450431, AI821410, AA493362, Z83819, AF127763, AF166328, AF166327, and AF166326.
HCQCR67	60	974592	1 - 662	15 - 676	AI522172, and AW026226.
HCRMC26	61	913972	1 - 731	15 - 745	AI609583, AA805672, AI076486, AW006108, AI708016, AA054347, AA063039, AA430074, AW294990, AA888790, AI014918, N57530, AI221602, AA579954, H91141, AA593129, AI828713, AW130274, AW162983, AI536783, AW163632, AW131695, AA541779, T99047, AW075255, R64176,

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HCRMJ47	62	919757	1 - 525	15 - 539	AB027466, AR035961, and AR035966.
HCRMP18	63	888719	1 - 620	15 - 634	AA853396, and AC005041.
HCRMIR08	64	958489	1 - 520	15 - 534	
HCRMIR69	65	877118	1 - 370	15 - 384	AI905014, AL040212, and AC005546.
HCRMT41	66	974324	1 - 632	15 - 646	AW392670, U46347, AL043003, AL043147, AL134132, AL042542, AW363220, AW384394, AL119457, AL134531, U46351, AL119324, U46350, and AL119396.
HCRND67	67	921398	1 - 1998	15 - 2012	AI978754, AA648498, AW001743, AI962419, AI446119, AI949312, N40531, AI522273, AA648907, W22178, AA773627, N46577, AI362932, AI214186, AA261979, AA252030, AW024768, AI935656, AW024010, AI416968, AI361764, AI039260, AA521447, AI127900, AI917267, AI761487, AA860961, AI936802, AI351462, AI580311, AI298481, AA931114, N26272, AI680734, AI864624, AW136987, W22807, AA808453, AA904280, N46583, AA131263, AA191430, H89921, AA326409, AI422420, AI189597, AI636058, AI680207, AA344413, AI767707, AA628794, AI312828, AW262532, AA860568, AA804488, N45139, AA574232, AI694810, T71336, AA251892, AI948498, AA364681, H91961, W22678, W22611, AA829581, T71491, H99173, N40538, and AC005325.
HCRNF63	68	916063	1 - 588	15 - 602	AA424352, AW297467, AI873546, and AI799462.
HCRNH81	69	914840	1 - 625	15 - 639	AW250326, C17590, AI278478, AW407305, AI278479, and

HCRNI04 HCRNK95	70	849408	1 - 523	15 - 537	AA128411, AW391907, W26388, R17779, and R17794. W96062, and W96061.
	71	890458	1 - 339	15 - 353	AA081839, AA310355, AA155876, H14728, Z45712, H18048, W67980, AA377062, H78474, H94833, AA359982, AA864236, F07871, N73165, N31384, H24503, AA504292, H25657, AA252782, F06229, AA309562, R52876, AI500636, and AI050265.
HCROE42	72	950701	1 - 878	15 - 892	AI701141, AW058533, AI458893, AW070453, AI435242, AI671435, AA912665, AI341202, AI243346, AW292434, AI373882, AI859938, AI203340, AI079549, AW167705, H05453, AI183877, AA737049, AI023804, AI831537, AI989594, N45293, AF142992, AF184344, AF177201, U94703, AF177202, and AF006072.
	73	974135	1 - 330	15 - 344	AI134524, AL119511, AL043152, AI431323, AI043168, AI432644, AI431307, AI431316, AL042853, AI431238, AI623302, AI866581, AI815239, AI432666, AI866786, AI567971, AI927233, AI440238, AI866465, AI494201, AW151974, AI500659, AI815232, AI801325, AI500523, AI538850, AI887775, AI582932, AI923989, AI590043, AI872423, AI284517, AI500706, AI445237, AI491776, AI289791, AW151138, AI889189, AI521560, AI500662, AI539800, AW172723, AI284509, AI582912, AI538885, AI440263, AI889168, AI866573, AI633493, AI434256, AI866469, AI805769, AI434242, AI888661, AI500714, AI284513, AI888118, AI285439, AI859991, AI436429, AI355779, AI889147, AI623736, AI581033, AI371228, AI491710, AI440252, AI860003, AI610557, AI431321, AI242736, AI828574, AI887499, AI539781, AI702065, AI539707, AI885949, AI285419, AW089557, AI559957, AI521571, AI537677, AI469775, AI804505, AI567953, AI815150, AI446495, AI866691, AI867068, AI952433, AI926593, AI285417, AI890907, AI432653, AI282249, AL042655, AI440260, AI955441, AI539260, AI042533, AW074057, AI225248, AI698352, AL043166, AI371229, AI358271, AL042787, AI432656, AI047611, AW151132,

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HCRON75	74	922386	1 - 186	15 - 200	AA040586, AI015787, AA938464, AA479214, AI282749, AA452413, AI799916, AA995903, AA902306, AW005485, AI302646, AA730505, AW192311, AW273459, AI868755, AI084500, AA182799, AI418984, AI278335, AA017529, AI241303, AA432193, AI004146, AW341825, AI400390, T40774, AI803455, W02777, AA354898, AI038039, AI469768, AI934274, AA013109, AI537782, AA877238, H07058, T48214, AA978013, AI911851, AA776891, AW304390, AW006644, N75836, AI084476, AA232952, AA479122, AI932697, AW196023, AI208222, F04445, F01828, AI130678, AW190128, T40963, AA644390, AA058919, AI122868, AI087324, AA369059, AA243728, AI561065, AI921425, AI828356, AA057173, N35151, AI597644, AI336533, AI620708, AA235996, N23222, AI816733, W60616, AA587281, AA954671, AI859497,

						AI357056, AW129922, N69671, AI066552, AI434169, AA194995, AA779835, C01287, AA243833, AA418568, AA418584, H43864, AA253056, H53350, R85536, R75653, W24835, AA629185, AA040558, AA789172, AA194809, AA535768, AA479121, and W07476.
HCROV23	75	975245	1 - 667	15 - 681		Z99396, AW392670, AW372827, AW384394, AL119457, AL119324, AW363220, AL119497, AL119522, AL036418, AL038837, AL119319, U46351, U46350, AL119341, AL119418, AL037051, AL036725, AA631969, AL119484, AL119391, AL119443, AL119496, AL119413, AL038509, AL119355, AL119483, AL119396, AL119363, U46341, AL037205, U46349, AL119335, AL036858, U46347, AL039074, AL036924, AL119401, AL134525, AL134536, AL119399, AL119444, AL037526, AL119439, AL037094, AL134531, AL037077, AL037639, AL042551, AL134538, AL134902, U46346, AL037082, AL036196, AL039564, AL037085, AL036767, U46345, AL038520, AL036190, AL036268, AL036998, AL036733, AL037615, AL037021, AL036238, AL037027, AL036765, AL036191, AL036679, AL036886, AL036158, AC005822, AR066494, AR060234, A81671, AR023813, AR064707, AB026436, and AR054110.
HCROZ66	76	909686	1 - 377	15 - 391		AA172248, AA327978, AA279942, and AL137710.
HCRPT92	77	931152	1 - 893	15 - 907		AA455567, AI459549, AA398062, AA515452, AI394051, AW044341, AA456064, AI699125, AA143102, and AA310438.
HCRPU05	78	931081	1 - 358	15 - 372		
HCRPZ11	79	973908	1 - 623	15 - 637		AL119319, AL042551, AL119418, AL119399, AL042542, AL043011, AL134518, U46341, AL119497, AL119401, AL119439, AL134528, AL042965, AL134538, AL119484, AL119363, AL119391, AL119355, AL119443, AL119483, AL042975, AL042896, AL119464, AL043029, AL039912, AL042544, AL042970, AL119496, AL042984, AL119304, AL043003, AR043113, AB026436, and A81671.
HCRQG35	80	954968	1 - 490	15 - 504		AW102682, AI051040, AI868693, W16730, AL134524, AL134110, AI142134, AL038983, AL037727, AL039643, AL045327, AL045328, AL039432, AL049018, AL047163,

AL037295, AL038838, AL037343, AI547295, AL042898, AL037436, AL037335, AL037323, AL037443, AL038532, AL038822, AL044125, AL037435, AL041347, AL040193, AL043923, AL043814, AL047012, AL041238, AL044186, AL040617, AL043845, AL038761, AL044162, AL040463, AL047170, AL044037, AL041635, AL040294, AL044064, AL041459, AL041577, AL043496, AL047219, AL040576, AL040625, AL040472, AL038651, AL045684, AL041752, AL045753, AL043538, AL040621, AL046850, AL040768, AL046994, AL046914, AL040052, AL041955, AL040444, AL040464, AL040510, AL043467, AL043677, AL040839, AL043492, AL041602, AL044074, AL041730, AL041523, AL043627, AL041374, AL043848, AL043570, AL047183, D29033, AL042135, AL041324, AW372827, AL046442, AL039360, AL041133, AL046392, AL045671, AL041098, AL039316, AL040322, AL041246, AL040119, AL044272, AL041096, AL044258, AL042096, AL041168, AL041163, AL041159, AL119324, AL045920, AL040148, AL047057, AL041296, AL040075, AL047037, AL037341, AL040458, AL044187, AL048677, AL041358, AL041292, AL041086, AL038745, AL045817, AL045990, AL040571, AW392670, AL041346, AL041142, AL040332, AL039338, AL079878, AL040529, AL079852, AL044199, AL041197, AL046330, AL044274, AL040745, AL041233, AL040370, AL040128, AL040553, AL040149, AL047036, AL040342, AL038878, AL041186, AL040414, AL039744, AL043941, AL041277, AL040285, AI318479, AL037279, AL040155, AL040091, AL044165, AL041131, AL040090, AL045989, AL119484, AL041051, AL040168, AL041344, AL043775, AL119439, Z99396, U46344, AL038024, AL040253, AL119418, AL041227, AL040082, AL036858, AL045857, AL135012, AL119399, AI547291, AL040329, AL119319, AL048714, AL119457, AL048657, AL047340, AW363350, AL134519, AL036767, AL119391, AL037094, AL134530, AL119443, AL036196, AW384394, AL119522, U46350, AL041278, U46347, AL043444,

					AL045494, AW363220, AL119497, AL042523, AL042544, AL119363, U46351, AL036190, U46349, AL119483, AL119355, AL036773, AL040263, U46341, AL038851, AL036418, AL038837, AL119341, AL119335, AL119396, AL040238, AL119444, AL037639, AL119496, AL037051, AL036725, AL1547258, AA631969, AL042420, AL042468, AL040255, AL037205, AL038040, AL045725, AL119464, AL134528, AR066494, AR064707, AJ238010, AR023813, D17247, A93923, A93916, AR060234, A81671, A93931, A85203, AB026436, AL133053, AR069079, AR054110, AL122101, and AR043113.
HDDAD23	81	967714	1 - 198	15 - 212	
HDDAF44	82	715802	1 - 550	15 - 564	H00541, W04294, AA909195, and AF055378.
HDRMA28	83	841936	1 - 316	15 - 330	AL1584176, AA024443, AA161492, H65697, H38769, T90477, AW236288, AI343169, AI364568, AA632907, AI719298, AW085811, AI735200, AI866580, AA586667, AC007676, AC007388, AC004983, AC006597, AC004796, AC007687, AL035072, AC005280, AL021939, AL021391, AC004526, AC004531, AC004491, AC004963, AL022476, AC005952, AL031577, AC005365, AL035695, AC005779, AC004381, AC003041, AC007666, AC005562, AL022398, AC004019, AC005412, Z84469, AC007878, AL109963, AL080317, AF196969, AL020997, AB023048, AP000689, AC004883, AC006141, AC009247, AC005095, AL133448, AC002350, AL050317, AF047825, AL034410, AP000501, AC005940, AP000555, AC005180, AC005026, AC002425, AC005071, AC006121, AC005531, AC006006, U62293, U63721, AP000133, AP000211, Z98742, AC006372, AC006455, AC006946, AC005701, AC005844, AC005057, AL079295, AL022067, AL117354, AC006538, AC007435, AC008115, AC007057, AC002538, AL139054, AL049872, AC004841, AP000356, Z95113, AP000563, Z83843, AL023284, AC006023, Z94161, AL049795, AC009248, AC005081, AF029308, AC004910, AR036572, U91328, AB003151, AL034400, AC005237, AC006323, AF064861, AC005529, AC005971, AL049778, AC007436, AL121658, AL121603, AC004386, AC006478,

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HDRMB41	84	691662	1 - 311	15 - 325	
HDRME31	85	697523	1 - 380	15 - 394	AL137191.
HDRMF01	86	915726	1 - 206	15 - 220	
HEPND10	87	963559	1 - 612	15 - 626	
HFLNA59	88	537447	1 - 305	15 - 319	AC002302.
HFLQA82	89	757380	1 - 126	15 - 140	AI075922, AI809982, AI381501, N51297, and AA937353.
HFLQF55	90	719018	1 - 976	15 - 990	Z43436, H59905, R12032, and D80088.
HFLSF55	91	955305	1 - 388	15 - 402	
HFLSH67	92	968639	1 - 350	15 - 364	AI299693, AA883901, AI191830, N55520, AI092823, AI913666, N77006, AI580351, AA995222, AA723196, AA885796, AA470715, AI311127, AC002312, AC005800, Z68162, AL022326, AB023050, AC007298, AC006006, Z84484, AC007312, AC002544, AC004887, AC004972, L78810, AC006965, Z84476, AL021939, AL049709, AP000031,

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HFSLJ23	93	509743	1 - 450	15 - 464	N63758.
HFSLJ61	94	507017	1 - 304	15 - 318	



HFLSK11	95	964908	1 - 451	15 - 465	AC007845, AC016025, and AC016026.
HFLSK31	96	535238	1 - 416	15 - 430	AI524810, AL031311, AC005288, AF190465, and AC005412.
HFLSK81	97	761133	1 - 401	15 - 415	H05992, AA525518, AL031584, AC005829, and AC002470.
HFLUF43	98	928026	1 - 840	15 - 854	AA341707, AA730474, AL035414, AC002365, AC004973, U82695, AL009172, AL031276, AC005211, AC005356, U07562, AF001548, AC006211, AL122003, U85195, AL031985, AC009516, AF024534, AC005086, AC010170, AC007298, AC007096, AC002119, AL031905, and AC004491.
HFLUF44	99	522416	1 - 443	15 - 457	W89038, AI762449, AI887272, AI924601, AW043702, AI800918, AF015308, and AF068007.
HFLUG50	100	526181	1 - 335	15 - 349	
HFLVE61	101	539872	1 - 380	15 - 394	T68764, X14690, X67055, and AC006254.
HFLVE85	102	531014	1 - 362	15 - 376	AB007954.
HFLVI15	103	921860	1 - 429	15 - 443	
HFLVJ52	104	954506	1 - 192	15 - 206	
HFLVBA62	105	754154	1 - 434	15 - 448	AA343433, AI248396, and AF090901.
HFLVGI78	106	935839	1 - 255	15 - 269	
HFLVGK74	107	789130	1 - 264	15 - 278	
HFLVHC25	108	678573	1 - 208	15 - 222	
HFLVHE45	109	572837	1 - 514	15 - 528	R24654, and AL031680.
HFLVHE66	110	572852	1 - 306	15 - 320	
HFLVHF81	111	929124	1 - 291	15 - 305	AA346826, and T60555.
HFLVHI01	112	916970	1 - 403	15 - 417	
HFLVHM86	113	572830	1 - 276	15 - 290	
HFLVHT75	114	573301	1 - 380	15 - 394	AA344780.
HFLVIH95	115	573198	1 - 445	15 - 459	
HFLVI133	116	871980	1 - 365	15 - 379	
HFLVBAE29	117	537309	1 - 289	15 - 303	AA343751, AA343713, and AA343517.
HFLVBAH38	118	503211	1 - 115	15 - 129	AA344168, AA343845, and Z98946.
HFLVBAH80	119	932630	1 - 216	15 - 230	AA343855.
HFLVBAI39	120	503055	1 - 362	15 - 376	AA343883.
HFLVBAI42	121	503057	1 - 446	15 - 460	AA345779, AA343729, and AA344370.
HFLVBAI44	122	536599	1 - 393	15 - 407	AA343730.
HFLVBAI70	123	707918	1 - 204	15 - 218	AA343886.

HGBAK23	124	500801	1 - 246	15 - 260	AA344764, and AA343998.
HGBAM36	125	509552	1 - 284	15 - 298	AA344076, AA344304, AA344477, and AC004168.
HGBAM75	126	509546	1 - 324	15 - 338	AA344134, AA345832, and AA323944.
HGBAN21	127	509538	1 - 308	15 - 322	AA344151, and AA344472.
HGBAO08	128	854321	1 - 206	15 - 220	AA344192, AA345549, W07336, AA564925, and M85967.
HGBAP09	129	509265	1 - 314	15 - 328	AA345977, AA344299, AW386937, and AC006323.
HGBAP42	130	509262	1 - 184	15 - 198	AA344282, and AA345692.
HGBAQ37	131	500799	1 - 266	15 - 280	AA344009, AA344267, and AA344356.
HGBAQ81	132	509533	1 - 210	15 - 224	AA344381, AA344514, and Y14489.
HGBAU10	133	961242	1 - 271	15 - 285	AA344397, AA237018, AA243581, AL079910, AI125886, AL047152, AW194322, W80416, N50796, H78664, AW009157, and H47038.
HGBAU93	134	625250	1 - 293	15 - 307	AA344601, and AA732430.
HGBAZ13	135	971646	1 - 345	15 - 359	AA344553, and AA344444.
HGBBB48	136	503470	1 - 289	15 - 303	AA344888, and AA345014.
HGBBO62	137	509691	1 - 623	15 - 637	N72651, N73115, AA345201, AF192522, and AC004938.
HGBBY74	138	509641	1 - 323	15 - 337	
HGBCH13	139	508982	1 - 292	15 - 306	AA345504, and AA345251.
HGBCU23	140	508807	1 - 307	15 - 321	AA346013.
HGBDB04	141	961510	1 - 375	15 - 389	W44483, AA035386, T35549, AA452722, AA057029, H69070, W32750, H49745, W76429, R72005, T30430, AA148014, W73817, AI080285, AW288085, T34177, AA147986, AA150156, W44484, AI085400, H73233, W72037, H49750, AI066753, N58555, AI826700, T34802, H50333, H46824, AI090058, AI885762, T89164, AI685629, T32128, F36442, AI361072, T35804, H47715, AI139439, AI720442, T34284, AA888074, AW026542, AI860947, H69218, AI363004, T35256, AI582271, T34182, R75697, T25347, N88560, AI744625, H72539, T31812, AA150040, AA579651, T30271, AA047370, T36153, AA782412, AI335748, N78151, T34116, D30929, H69063, AA035385, AA248079, AI761650, AA301051, AA369356, F36921, C05196, AA862651, AA830645, AA431325, AA090035, H72938, H69071, AA579160, AI826369, AW364000, H48067, AI394420, AA669621, F26842, H99978, AA938754, H49513, AI261333,

					C04184, AA862374, AA748804, H74239, AA887224, AI769256, AA568518, AW182004, AI219387, H46745, AA037011, AA669683, R72006, AI220761, F18095, H69064, AI582096, AI150900, AI358853, AA923809, AI184113, AI002474, AI093342, AI367456, AI097516, T63027, AW363987, H50450, AI363806, W32693, AA125944, AI015971, AA972455, AI302031, and H49518.
HGBDB21	142	753848	1 - 356	15 - 370	AA534444, and AA344632.
HGBDC48	143	960971	1 - 406	15 - 420	AA345950, AA343937, AA346012, and AA344317.
HGBDD52	144	954496	1 - 544	15 - 558	AI446018, AA343716, T80849, AA344417, AA345708, T80924, and AI049839.
HGBDE16	145	533741	1 - 464	15 - 478	AA568404, AC004106, AL049591, Z98946, and AC005094.
HGBDF61	146	742234	1 - 441	15 - 455	R59319, W25783, T80460, AA345654, and AC006959.
HGBDG59	147	522932	1 - 358	15 - 372	
HGBDG69	148	578390	1 - 342	15 - 356	AA447829, and AL137370.
HGBDH63	149	732530	1 - 257	15 - 271	
HGBDI95	150	509439	1 - 319	15 - 333	AA345826, AA344598, and AL096701.
HGBDL05	151	932881	1 - 748	15 - 762	R91010, AA718934, and AA345915.
HGBDL72	152	710318	1 - 362	15 - 376	AA345940, and AA345679.
HGBDU57	153	731004	1 - 113	15 - 127	AW026322, D44839, and X77631.
HGBDX24	154	678576	1 - 469	15 - 483	AI767326, N51939, AA029906, AA030035, AI242673, AI341053, AA931042, AA877157, AW172418, AW384993, R70208, N46437, and AC004945.
HGBDX35	155	503477	1 - 353	15 - 367	AA343767.
HGBDY02	156	921081	1 - 271	15 - 285	
HGBDY30	157	503476	1 - 225	15 - 239	AA343777, and AC007298.
HGBDY59	158	815818	1 - 442	15 - 456	AI685090, AI904421, E14558, and E14559.
HGBEY32	159	971570	1 - 295	15 - 309	AA343864, and AC005244.
HGBGA29	160	508433	1 - 216	15 - 230	AA345731.
HGBGI54	161	573764	1 - 257	15 - 271	AA345642, AI524488, AI373756, AI498126, AW055308, H21096, AI650514, and AI655067.
HGBGI57	162	573752	1 - 321	15 - 335	AW302143.
HGBGO22	163	558830	1 - 345	15 - 359	T28629, and Z11502.
HGBGT92	164	924780	1 - 315	15 - 329	

HGBGW04	165	573644	1 - 322	15 - 336	AC006529.
HGBHC35	166	573687	1 - 302	15 - 316	AF039186.
HGBHM09	167	573673	1 - 250	15 - 264	
HGBHN46	168	573678	1 - 228	15 - 242	
HGBHP95	169	781326	1 - 290	15 - 304	
HGBHS11	170	967385	1 - 213	15 - 227	
HGBHY06	171	937940	1 - 434	15 - 448	T87025, AL045919, AI926049, AI826890, AA468860, AA612729, AA654159, AA171760, AW197994, AI272783, AA172001, AI308822, AI674148, AI379842, AI582837, AI889712, AI828370, AI199276, AW188430, AA704757, AA536162, AA573761, and AI300550.
HGBIC81	172	796500	1 - 94	15 - 108	
HGBID55	173	575197	1 - 298	15 - 312	AA344805, AI911569, AA082564, AI003260, AI244141, AI026132, AL034408, AC004038, and AC005702.
HGOCB25	174	506771	1 - 335	15 - 349	AA346046, AA345869, AA468975, AA847499, AI250552, AI251034, AI254770, AI284543, AI054090, AA664126, AA053463, AI251284, AI251203, AI223626, AI249853, N27874, AI734155, AI302350, AA557136, AW303098, AI246061, AA572987, AA487209, AI251241, AI251944, H69661, AA565911, AA468494, AI679294, AW083706, AA601396, AA468956, AW276678, AI076328, AL049761, Z99716, AL022165, AP000689, AB003151, Z98946, AC002404, AC005921, AL021707, AC004129, AC005284, AC000066, AP000022, AF196779, AP000163, AC006130, AJ010770, AC007226, AC002430, AL117340, Z93020, Z95114, AC007384, AF047825, AC007388, AC005180, AL035071, AC007371, U95740, Z99127, AP000117, AL031311, AC007227, AL031584, Z86090, AC006059, AC005071, AC005953, Z84487, AC005280, AC004253, AL031774, AL050318, AC005746, AC004491, AC004966, AL031597, U63721, AC003982, AC007566, AP000704, AC007327, AL109627, AL022326, Z98752, AC003070, Z99129, AL049833, Z84469, AC005081, AL109963, AC006965, AC009248, AL096773, U91323, AC005014, AC005821, AL035405, U95737, AC005736, AC007221, AC006449, AC005696, AC006014, AJ003147, U07563,

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HHLBA18	175	527530	1 - 287	15 - 301	AA309288, and AA309302.
HISAC25	176	678054	1 - 550	15 - 564	R83066, H88059, and T19075.
HISAI35	177	707172	1 - 349	15 - 363	
HISAM61	178	974576	1 - 718	15 - 732	
HISAN16	179	661752	1 - 362	15 - 376	AI762464, H96353, W52333, AW005759, AI567449, W52311, AA417658, C06018, H85374, AF070666, and AF228418.
HISAN47	180	710943	1 - 306	15 - 320	AA205399, H25580, D45750, AW156895, AI452450, AW263536, and U55184.
HISAT61	181	488809	1 - 360	15 - 374	
HISBA01	182	916165	1 - 353	15 - 367	
HISBB09	183	964344	1 - 378	15 - 392	AA719847, AA069254, and AC005215.
HISBB67	184	751467	1 - 397	15 - 411	H79323, AA628627, AL031668, L78833, AC004832, AC004960, Z86090, AL023802, U73630, Z98752, AL031276, AP000556, AL023799, AC008115, Z98272, AC007253, Z81450, AC004973, AC004913, AC004668, AC003982, AB017602, AC002039, AC004916, AL023803, AC005940, Z95152, AC005202, AC003687, AP000557, AP000552, AC004812, AC007543, AC005411, AC003963, AC004811, and AC006009.
HISBE32	185	677148	1 - 458	15 - 472	

HISBG13	186	657005	1 - 388	15 - 402	T88699.
HISBH10	187	964359	1 - 432	15 - 446	
HISBJ96	188	796306	1 - 328	15 - 342	
HISBO64	189	745884	1 - 406	15 - 420	AW117195.
HISBT02	190	919509	1 - 447	15 - 461	AW264600.
HISBU45	191	717604	1 - 681	15 - 695	AA417810, and AW103464.
HISBU68	192	693115	1 - 382	15 - 396	
HISBW20	193	669525	1 - 639	15 - 653	H85310, AW020413, AA813343, and AI806413.
HISCF72	194	740183	1 - 408	15 - 422	AW173015.
HISCH85	195	761973	1 - 518	15 - 532	AA627075, AA631714, AI479807, AI359396, AA528184, AI860932, AI828517, AA947640, AI609019, AI829984, AI560408, AI719121, AI420471, AI698992, AI041652, AA622678, AW072220, AW243981, AW025818, AA287630, AA983885, AW275394, AA604879, R72570, H63981, H24824, AI864546, AA887706, AI700883, AI475364, AA579648, AI183273, AI205801, AI867829, AA531533, AA994860, AA953158, AA588021, AA436860, AW050606, AA974927, H42312, AA442617, AA282509, AA347744, AA931153, AA651826, AA994191, H02868, H87783, AI524119, W74308, AA773196, AI458825, AA576762, AI632938, AI973009, AI440250, AI632950, AI738914, AA573307, AA523385, AA523403, AW028760, AI829899, AI573013, W19381, AI359895, H00155, R22801, AA579577, R16093, T69750, AW170108, AI827077, R15727, AW194872, H24777, AA743192, AA286723, N92795, AI000057, H22337, and R24453.
HISCL83	196	831507	1 - 476	15 - 490	AA025795, and AA025796.
HISCK85	197	857497	1 - 463	15 - 477	
HISCL06	198	935079	1 - 439	15 - 453	M77899, AA834297, T16056, AA132914, H50834, AA347170, F09736, F01141, AA368679, AC005100, L44140, L43392, AL078621, AF060568, U67274, U20770, AC007314, AP000302, AP000114, AP000046, X58156, AF193806, U55180, AC006137, AL021392, U07000, AP000010, AC005356, AC006480, AP000431, AP000563, AP000211, AP000133, and AC005082.
HISCN24	199	764837	1 - 417	15 - 431	R69549, AW300639, AA630465, and AL034430.

HISCP11	200	966171	1 - 390	15 - 404	
HISCV30	201	883892	1 - 736	15 - 750	N64812, and N75663.
HISDM43	202	974583	1 - 681	15 - 695	AA890180.
HISDO59	203	857479	1 - 867	15 - 881	AA327184.
HISDS91	204	787603	1 - 442	15 - 456	AW294889, W95876, AW026465, AI371099, AW103708, D60327, and AC003090.
HISDT82	205	790966	1 - 550	15 - 564	
HISDU39	206	745914	1 - 520	15 - 534	
HISDV63	207	788753	1 - 362	15 - 376	
HISDZ80	208	775474	1 - 556	15 - 570	AP000066.
HISEA07	209	952295	1 - 320	15 - 334	H05255, and AC004104.
HISEE71	210	759828	1 - 418	15 - 432	
HISEJ18	211	783919	1 - 328	15 - 342	
HISEJ39	212	789809	1 - 398	15 - 412	
HISEN88	213	760209	1 - 493	15 - 507	
HISES80	214	775598	1 - 427	15 - 441	AC007358.
HILDAK38	215	689904	1 - 445	15 - 459	
HILDBF84	216	924101	1 - 1354	15 - 1368	AI057008, N54429, N68450, W02198, N73582, H55898, N91067, H61872, H60652, H64326, AA342972, T68527, H65614, AI651926, AI248786, T68461, T53810, N91293, T90818, H59838, H91121, AW241535, H54060, H89498, H60134, AA344190, T53934, T85721, H60133, H54059, H82326, H65615, AI651938, N63663, and N74009.
HLDBJ86	217	882365	1 - 440	15 - 454	AI016020, and AF097518.
HLDBR32	218	752494	1 - 537	15 - 551	
HLDC51	219	871341	1 - 376	15 - 390	
HLDCG82	220	657567	1 - 530	15 - 544	AC002553.
HLDCI35	221	831356	1 - 761	15 - 775	AI760643, T78476, AI913746, N74639, AW450191, R99475, AI672811, T71577, N58369, AW444631, T40936, T91004, T78557, R99474, R28738, R93411, T81723, T84581, AW300983, T82031, and AF209192.
HLDCU27	222	950724	1 - 304	15 - 318	
HLDDH01	223	926360	1 - 333	15 - 347	
HLDDI91	224	790003	1 - 594	15 - 608	N77737, AA577996, AA678055, and AF209192.

HLDDK12	225	923442	1 - 405	15 - 419	AC007878.
HLDDL55	226	875000	1 - 442	15 - 456	AI420986, AA558494, AA742449, AI264145, AA582499, AA954657, AA908360, H30455, AA456055, AI991352, AL047763, AW071417, AI445025, AL036146, AI349933, AI250293, AI340582, AL135661, AI702406, AW071349, AL046849, AW195957, AI540832, AI613017, AI439087, AI678302, AI568870, AI249257, AI500077, AI207510, AI702433, AW274192, AI868831, AI498579, AI433976, AI866608, AL121270, AL036396, AW238730, AI499463, AI349645, AI064830, AL047042, AW303152, AI800453, AI800433, AI538716, AI633419, AI866002, AI568855, AW169653, AL048871, AW301409, AW103371, AI349772, AI590128, AI349004, AI433157, AW074993, AI349614, AI699857, AI445432, AI857296, AL045903, AI635461, AI625079, AI440426, AL036802, AI312152, AI597750, AI758437, AI349937, AI521012, AI275175, AI281779, AW074869, AI224992, AL040243, AI564719, AW148320, AI567351, AI620284, AI343112, AW268253, AL045500, AL119791, AL036274, AI345735, AI866887, AW089572, AW162071, AW068845, AI687728, AL043326, AI497733, AI434281, AI687375, AL121365, AI499131, AL119049, AI500553, AL038605, AI673256, AL036361, AI348897, AI873731, AI863014, AI349256, AI636456, AI439745, AI282655, AI440239, AI800411, AI690751, AI281773, AL036759, AW085799, AI811863, AI269696, AI969601, AI269205, AI568854, AL036980, AI686926, AI567632, AA508692, AI366549, AL038779, AI631107, AI610645, AI570384, AI624668, AA572758, AI753683, AW117882, AI539771, AI636445, AI815383, AW002342, AI697137, AI281762, AI469811, AI969567, AI499393, AI818683, AI920968, AI436456, AA613907, AI271786, AI569616, AI285735, AI608667, AA640779, AI682841, AW087445, AL038778, AI446628, AL119748, AL121014, AI475371, AI620868, AI690835, AI687376, AI469532, AI679724, AI610307, AI580190, AI475134, AL121463, AI343059,



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HLDN157	227	733903	1 - 406	15 - 420	R09042, and N66008.
HLDNU53	228	883158	1 - 779	15 - 793	T79293, AW299681, AA777852, AA705161, T68667, AI928177, N59580, and AF097518.
HILDOA63	229	949166	1 - 509	15 - 523	T46901, and T74588.
HILDOB53	230	728220	1 - 300	15 - 314	AC005320.
HILDOG86	231	682265	1 - 297	15 - 311	N76019, and C21130.
HILDON90	232	788891	1 - 691	15 - 705	H54384, AW021286, AA548081, AA704453, AA728877, and AA715354.
HILDOR73	233	683262	1 - 280	15 - 294	AA484455, and AF153821.
HILDOU12	234	857106	1 - 544	15 - 558	AF202889, AC007707, and AF202890.
HILDOZ69	235	697988	1 - 686	15 - 700	U73330.
HILDPA63	236	744341	1 - 315	15 - 329	H55681, AI084348, AJ230815, AW270278, AA737444, H61631, AI355513, N41806, AA584482, AA584101, N33867, AA555244, T51930, AA150598, H68042, AI272241, H15652, AA747377,

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HLDQA88	237	796173	1 - 285	15 - 299	Z54728, and Z54729.
HLDQB65	238	708002	1 - 437	15 - 451	AI090052.
HLDQC62	239	923559	1 - 1340	15 - 1354	H62757, AA778222, H47743, R98624, H60487, and H54740.
HLDQH10	240	932015	1 - 510	15 - 524	N56664, and AB023136.
HLDQQ76	241	953312	1 - 524	15 - 538	AI093928, AI439848, T50791, AW449664, T68870, AI623302, AI431307, AI431316, AI431238, AI432661, AI432666, AI432655, AI432644, AI431235, AI432657, AI431246, AI431350, AI431347, AI432653, AI431323, AI431231, AI431230, AI431257, AI431321, AI431318, AI431315, AI431328, AI432654, AI431310, AI431312, AW081103, AI432650, AI432677, AL045494, AL042523, AI431247, AI431354, AL042729, AI431353, AI492519, AF086735, Y17793, and AF019249.
HLDRD44	242	697576	1 - 921	15 - 935	AI335086, AI302888, and T40004.
HLDRE54	243	727954	1 - 251	15 - 265	AC005668, and AC005233.
HLDRE26	244	681284	1 - 531	15 - 545	R70015.

HLDRE66	245	966517	1 - 238	15 - 252	
HLDRJ94	246	784582	1 - 384	15 - 398	AW002504, AI962026, AI955061, AI828858, AA489230, AI203414, AI097549, AI422926, AI355971, AW195500, AI423708, AW001625, R07167, and R07166.
HLDRP14	247	657908	1 - 677	15 - 691	W31702, AW303472, AA834684, AC007242, AL034375, AL008627, AP000304, AP000047, AP000115, AC004998, AB020877, AC008078, Z97352, AC004531, AC008125, AL023803, AL118512, Z97206, and AC008045.
HLDRQ82	248	837031	1 - 773	15 - 787	AI209097, AI073500, AI744810, AI218488, AA312659, AA400307, AA779312, T50722, T72192, T69305, T50877, AA401562, AA745947, AI240480, T74831, AI024280, C21015, T74746, T72971, and AF064255.
HLDRR54	249	708594	1 - 349	15 - 363	
HLIBJ35	250	870387	1 - 598	15 - 612	AA682991.
HLIBJ13	251	910830	1 - 409	15 - 423	AW299514, AI796131, AW299658, AW058550, AI767984, and AF152562.
HLIBO03	252	923519	1 - 302	15 - 316	
HLIBP66	253	750608	1 - 219	15 - 233	
HLIBZ48	254	721023	1 - 331	15 - 345	W90538, and AA345641.
HLICR73	255	837030	1 - 485	15 - 499	T69381, AI765674, Z20524, AW025169, AI565556, T72971, AL042852, and AF064255.
HLICT47	256	929754	1 - 342	15 - 356	
HLICT57	257	734451	1 - 486	15 - 500	
HLPBD66	258	928708	1 - 516	15 - 530	AW118937, AI123209, AW001864, AI377932, AI912990, AI805972, AI651420, AI285856, AI141443, AI673052, AI221575, AI743946, AI760176, AI754531, AA026012, AI660528, AI949710, H19313, AI249502, AI460280, R77684, AA026000, AA829761, R77685, AI687732, AI812062, AA084602, C21025, and AF147395.
HLQAF70	259	529348	1 - 291	15 - 305	
HLQAL33	260	702755	1 - 428	15 - 442	R80289, and R34778.
HLQAN64	261	966910	1 - 620	15 - 634	AI052592, AI052580, AA928708, H56001, R97419, AW242444, H57112, AF090318, and AF090320.
HLQAZ69	262	960046	1 - 288	15 - 302	AW392897, AL021920, and AB007923.

HLQBF72	263	608371	1 - 354	15 - 368	AW136027, AI634613, AW082330, AA995665, AA292087, AI201246, AI693706, AI675765, AW390785, AA868564, AI654869, AW390814, AI077669, AI695580, AI805189, AC004893, and AF199364.
HLQBH46	264	527923	1 - 369	15 - 383	
HLQBI21	265	529342	1 - 733	15 - 747	AI913732, H70488, C20914, AL121739, AL021879, AF104312, and AB024079.
HLQBL71	266	542262	1 - 196	15 - 210	
HLQBX13	267	856783	1 - 209	15 - 223	
HLQBX23	268	676205	1 - 318	15 - 332	
HLQCN58	269	706239	1 - 425	15 - 439	T19011, AB003151, and AP000688.
HLQCY26	270	681459	1 - 257	15 - 271	
HLQDB55	271	731601	1 - 376	15 - 390	
HLQDC82	272	779697	1 - 661	15 - 675	AA056145, AI889521, AI422011, AA677596, AI831767, AA463625, AI670807, AA639920, AI262820, AA502322, AA428450, AA029914, AI580188, AA443521, N71012, AA171922, Z41654, AA629920, AI217583, H66183, AA443042, AA030044, and AC005996.
HLQDE61	273	741706	1 - 345	15 - 359	AC007529.
HLQDPI1	274	966775	1 - 343	15 - 357	AI671077, AI679294, AI679871, AI567391, AI273837, H29241, AA558404, AA564642, AA847499, AI281622, AI539822, AA649274, AC006065, AI022311, AC005197, AC005837, AC004477, AF047825, AI022318, AF196969, AP000300, AC006449, AF053356, AI034420, AP000501, AC005015, AC005412, AP000045, AI031311, AC007993, AD000092, AP000113, AI035072, AC005488, AC002316, AC005231, AP000102, AI049759, AC004596, AC005730, AP000248, AC005318, AC007537, AC005527, AI050306, AI049776, AI050318, U63721, AC005775, AI121655, AI031587, AC002544, AC005529, AI080243, AC004821, AC004491, AI031283, AC005082, AP000049, AC005081, AC007347, AC004019, AC002395, AC002425, AC004972, AC002991, AC004605, Z83844, AP000311, AC005071, AC006014, AC005839, AC003982, AI133163, AI031291, AC003030,

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HLQDU40	275	488692	1 - 311	15 - 325	AA827683, AA584644, AA731210, AA837295, AA836453, and AA287331.
HLQDY10	276	856755	1 - 461	15 - 475	AA720741, AL042373, AA351868, AW029626, AI888050, AI114755, AA565534, AC005911, AC005253, AL022165, Z75887, AL049709, AC007057, AL049872, AC005624, AL021707, AL121915, AC007686, AC005529, AC004881, AL133382, AC003042, AC005280, AC006285, AC004448, AC007129, AF053356, AC002350, AL035451, AL031677, AC004019, AC003665, AC006538, AC003682, AL022393, AL117352, AL022721, and AL096791.
HLQED11	277	966015	1 - 281	15 - 295	AA357240, AA626678, AA515435, AA377730, AL036706, AA843450, AL572560, AA633936, AI148446, AL039958, AI284640, AI053672, AW419262, T56067, F25276, AI954260,



F36273, AI937850, AI334443, AA468486, AA776971, AA302523, AI610159, AI564185, AA330380, AA810318, AW193265, AW302907, AL046457, AW340922, AA514819, AW390126, AW102955, AL119391, H64777, AI561060, AA595782, AW074398, F32894, AI889923, AA017322, AL138455, AW338869, AA513972, AA632563, AA084070, AA621858, AI499938, AA630925, F32926, AA919037, AA325699, AI653886, AA627160, AA508080, AA489775, AA434484, AA491762, AW069481, AC005072, AF006752, AC005730, AC002553, AC005184, AC018633, AC006195, AC007536, AC005488, AP000077, AC005242, AC005993, AP000502, AC004919, AC006012, AC005191, AC005837, Z70224, Z49258, AP000302, AL031005, AC010202, AF134726, AL031056, M87918, AL050348, Z98950, AP000114, AP000046, AC004485, AF067844, AC005082, AC006115, AC008044, AL049759, AL021155, AC005037, AC000159, AC005726, AL031176, AL035658, AC004854, AC007447, AL049869, AP000141, AC008134, AP000193, AP000049, AC007043, AL008725, AC005544, AC005231, AP000311, AC006019, AL049757, AL035417, AC005043, AC006167, AL034554, U85195, AP000117, AC011311, AC006312, AL031255, AL078603, AP000146, AC006111, AC004963, AC004087, AL031985, AL079340, AC006449, AE000658, AL050306, AC004184, AL035045, AC007537, AF196969, AC005755, AL049699, AL034417, AF002223, AC007981, AC009178, AC006207, AC002491, AB003151, AB023050, AL022318, AL031387, AC007055, AC005288, AF108083, Z84572, AC005355, AC007666, AL049761, AF205588, AC005083, AC002476, AL009181, AC005972, AL031774, AC004858, AF109907, AC005023, AC002379, AL133289, U58675, AP001116, AP001172, AC006479, AC007630, AC006211, AC005066, AP000511, AL031721, AC004019, AC006432, AL117351, AC000052, AF064858, AL031289, AC008079, AC006538, AL109827, AL049780, AC005264, AC007676, AC004682, AC008372, AC006511, AC020663, AC004098,					
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HLQEH54	278	871683	1 - 641	15 - 655	AC002395, AC008072, AF039590, AC005912, AC005829, AL031224, AC005324, AC004859, AC005081, AC005015, AC004828, AC006274, AC005594, AC003983, and AC002984.
					AI935557, N53561, AI435571, AI628733, AW104342, AI950465, H57932, N91619, AA701378, AA410255, AI056635, W86579, AA705304, H58023, R85396, N68729, AI492415, T54915, AI239546, AA928077, AI910761, W86712, AI076347, AA406529, AW299867, T95811, T95812, AA689340, T55082, N72520, R59629, F09287, and AL109938.
HLQES58	279	856725	1 - 538	15 - 552	AC003034.
HLQEX16	280	856712	1 - 406	15 - 420	
HLQFD23	281	856701	1 - 467	15 - 481	
HLQFO69	282	933385	1 - 851	15 - 865	AI378007, AW118802, AA703945, AW117265, AI023239, AI887376, AI819938, N32787, AA858163, AI304385, AA815054, AI859862, AI810059, AI393415, AA948491, AI886088, T62800, AI123750, N41789, AW183288, AI300250, AA838276, AA092069, AW264818, AA070204, and AA922124.
HLQKG74	283	856736	1 - 1023	15 - 1037	AA777852, AA705161, AI042209, AI928177, AI654148, AA813350, AW295882, N53049, AI470632, AA740656, T79206, N69913, R37797, N57759, N73233, N53068, N74422, N53052, N59580, N73255, T68587, AA699764, R12776, AA211797, AI022232, T16909, R00599, N73237, AA720617, R00498, T69188, T69130, N74370, AA720618, AW237757, AA702356, AW299681, T79293, and AF097518.
HLQGN56	284	842004	1 - 529	15 - 543	AI264223, AI742821, W51908, AI344621, AI244990, AI090358, H66320, N52269, W04231, H66367, AW024722, AI189682, AW238594, AA599354, AW021399, AA515733, AA482928, AA485831, AA487209, AA516193, AI206841, AA199578, AA977307, AI719142, AI567676, AI245693, AA347203, AA807921, AA627921, AA631146, AA598608, AC005082, U95742, AC003982, AL022238, AC007386, AC006512, AC005015, AC006064, AC005755, AC004000, AC002476, AL035659, AC002302, AC007637, AF000692, AC006344, AL022333, AC004771, AC004804, AC005377, AC005480, AP000552, AF190465, AL049757, AC005412, AC007199,

AP000547, U91321, AC004796, AC004465, AC004895, AC005914, AJ010770, AL049872, L78810, AC007066, AC004953, AC006001, AC004217, AL117340, AL031291, AC006571, AC004815, AC007917, AC012384, AL121658, AL031230, AC004526, AC003684, AC002375, AC006965, AC004797, AC004859, AC005409, AC007371, AC006960, Z93930, AL049759, AP000248, AC004552, AF205588, AC006277, Z98304, AC005482, AL096701, AC005049, AC004167, AL139054, Z82198, U85195, AL049709, AC002430, AC007050, AC003665, AC005722, AC006236, AF001549, AC004477, AC003108, AC007057, AC007225, AC004983, AF111168, AC007216, AL031311, AC006530, Z97181, AL021578, AC005519, AC005071, AP000555, AC006111, AE000658, AC007384, AC006101, AL133445, AC005969, AC004913, AC006480, AC005066, AP000556, AC002477, D87675, AC005245, AL020997, AC005921, AC005180, AC005740, AL035423, AL133246, AL049694, AL031295, AL034555, AC005037, AL049830, AC009464, AC006441, AC005971, AC005207, AP000113, AP000512, AC002429, AC005878, AC002470, AL035461, AC002041, Z95113, AC004019, AC005620, U96629, AC005771, AC007065, AC004673, Z93023, AC004974, AP000116, Y10196, AC006039, AL031281, AF067844, AL096791, U91326, AL021808, AC005486, U47924, AC005244, AL049776, AC005696, U80017, AP000151, Z99943, AF200465, AC002553, AL096678, AC005102, AC006077, Z98884, AC006581, Z98749, AL117338, Z97054, AL023553, AC009721, AC007731, AC005678, L78833, AC005011, AC010582, AC002351, AL049869, AC008372, AC006544, AC005154, AC005393, AC005924, AC005031, AJ010598, AL133241, AC007686, AL121653, AL031284, AP000359, AC005225, AC005065, AC005730, AC005598, AC002544, AC005844, AL022329, AC004033, AC006317, U52111, AC005399, AL035455, AB020868, AC010197, AC006486, AC005295, AC002036, U63721, AL080243, AL031846, AL109963, AL031666, AC009516, AP000510,				
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HLXTF06	285	931101	1 - 281	15 - 295		
HNAAA40	286	574045	1 - 344	15 - 358		
HNAAE33	287	574001	1 - 176	15 - 190		
HNAAE73	288	922929	1 - 336	15 - 350		
HNALD49	289	723168	1 - 597	15 - 611		AA405939, AL110219, AF190862, and Z83844.
HNJBA08	290	955993	1 - 1597	15 - 1611		AA026755.
						AA026793, AW371970, AI149147, AI962386, N57426, AW295290, AW341196, AA811125, AA973041, AW025864, AW375504, AI078419, AW269550, AA281527, AI858149, AA831209, N32331, AI087365, AI000710, AA971571, AW275545, AA936889, AI767131, H94323, AI818072, N48251, H96360, AI301505, AA281528, AA749459, AW170509, AI160322, AI362012, AA954535, AA515033, AA584953, HI3510, AA700795, W81370, N94553, H79658, AI799151, H96359, AW192808, AI014406, AI928296, AA451944, AA312205, W81628, W30844, AW015967, AA451984, AI767192, AI638443, R25745, T86900, W30890, H79659, AI383042, AA356792, AA995999, AA487287, AW393332, AA730481, AW058463, AA095644, AA294847, AW375501, AI247784, AA174181, AI459049, AA032012, AW264654, AW339209, and A63552.
HNJB04	291	927458	1 - 296	15 - 310		
HNJB08	292	947047	1 - 523	15 - 537		T79589, AI056960, AI084845, AW297063, AI368169, AI924527, AI924182, AI597567, and AW271159.
HNJBL71	293	939266	1 - 609	15 - 623		AI608603, AW352295, AW238519, AI767967, AW085774, AA863266, AW117932, AI310728, AA865790, AA864183, AI141812, AF081497, AF193809, and AF185277.
HNJBN94	294	948996	1 - 738	15 - 752		AI121756.
HNJBW16	295	955920	1 - 542	15 - 556		
HNJCD23	296	961494	1 - 280	15 - 294		
HNJCH53	297	969065	1 - 1279	15 - 1293		AW003768, AA148418, AI287784, AI802530, AI922026, AI620677, AA148419, and AW129759.

HNJEA92	298	955842	1 - 1111	15 - 1125	AI828943, N23239, N27741, AI873442, AI311608, AW207380, AW292495, and AA315985.
HNJEC12	299	969099	1 - 847	15 - 861	AI097310, AI831788, AI680822, AA150619, AI681082, H21871, AA150789, H21870, H44088, AI696270, H26257, AI192339, H44023, AI767250, AA025148, and AI023582.
HNJFC68	300	956178	1 - 483	15 - 497	AA743820, AA760673, and AA883200.
HNKBB44	301	955843	1 - 826	15 - 840	AI828943, N23239, AI873442, N27741, AW207380, AI311608, and AW292495.
HNKBR49	302	955844	1 - 470	15 - 484	N27741, AI311608, AW207380, AI828943, N23239, AW292495, and AI873442.
HNKBS78	303	955565	1 - 786	15 - 800	AI828943, N23239, AI873442, N27741, AW207380, AI311608, and AW292495.
HNKBV10	304	961542	1 - 439	15 - 453	
HNKCF21	305	951659	1 - 1457	15 - 1471	AI857688.
HNKCG51	306	933428	1 - 963	15 - 977	AA195092, AI805891, AW082197, AI139415, AA745263, AA744624, AA195050, AA459075, AW204020, R95745, AA278326, and AA278997.
HNKDV89	307	963354	1 - 772	15 - 786	AI954729, AI359495, N51083, AI948741, AA935553, AA779869, AA935556, AW449916, AA405449, AA664730, AI247429, AA769001, N50097, N54209, AA552736, Z38366, C14601, D59921, AI537677, AI036265, AI648663, AI439717, AI922901, AI702406, AI591316, AI554427, AI868831, AW262565, AI866608, AI043326, AI500039, AI610756, AI872711, AI682743, AI520785, AI633419, AI921248, AI491852, AI610645, AI049085, AI036361, AI498579, AI475371, AI119791, AI249257, AI273048, AI536685, AI269205, AW104724, AI624206, AI811344, AI637584, AI857296, AI926790, AI564719, AI889376, AI524671, AI274013, AI500146, AI571909, AI619502, AI802542, AI828731, AW026882, AW087445, AI862144, AI433157, AW169671, AI567128, AI702073, AW150578, AI539771, AI682841, AI560099, AI538716, AI344817, AI250293, AI636445, AI036736, AW132056, AI696612, AI890833, AI048871, AI079963, AW403717, AI690751, AI349004, AI433976, AI224992, AI539153, AI570909, AI648509, AW268220,

AI287489, AI612759, AI580240, AW103371, AI567993, AI680280, AI567351, AI554484, AW088793, AW008048, AI912866, AL045500, AI799199, AI815855, AI801766, AI702068, AI284020, AI888501, AI800453, AW168795, AW238730, AI919345, AI439745, AI859511, AI569616, AI701074, AI636456, AI536638, AI289937, AI569583, AL040243, AI274508, AI474107, AL047763, AI783504, AI620284, AI612920, AW196141, AW301409, AW078529, AI521012, AI690312, AI571551, AI570384, AW002342, AI475451, AI824557, AI702433, AI273142, AW082040, AI613017, AI572676, AI434281, AW103893, AI561299, AI269696, AI445165, AI590120, AI866002, AL036274, AI445025, AW148716, AI431975, AI679504, AI648684, AL038069, AI815232, AI835801, AL036403, AI686597, AI573032, CI6221, AW085799, AI362637, AW162071, AL121328, AI636719, AI349933, AI800433, AL038605, AI568296, AI281779, AI559296, AI497733, AI432969, AI572787, AW169653, AI921244, AL121365, AI500523, AI871697, AA640779, AW129202, AI590227, AI677796, AI269862, AL038645, AI492528, AI687065, AI612721, AL135661, AI538259, AW071349, AW149869, AW118512, AW131954, AI521040, AI567940, AW118398, AW102785, AI499131, AI285735, AI625079, AI538829, AI969601, AI866457, AI690426, AI630928, AI270707, AI275175, AI281837, AI612913, AI440239, AI271786, AI308032, AI635461, AI690480, AL036146, AI282281, AL036759, AW075351, AI684279, AW080402, AI097248, AI668893, AW080327, AI869367, AI590999, AI445432, AW148320, AI784252, AL039086, AI468872, AW129170, AW075413, AI590128, AI274541, AI500077, AI568870, AL038565, AA427700, AI590118, AI680165, AI308035, AI934035, AI580984, AI925156, I48979, AL110196, AB019565, AF113690, I89947, I48978, AL050277, AL137557, A08916, AF017152, AF113019, S68736, I89931, AF090934, AL133640, A08913, AF104032, S78214, AL122050, AF078844, AF111851, Y16645,					
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AF113691, AL133075, AL050149, AL080060, X84990, AF113676, AL117460, AL050116, AF079765, AL122121, AF106862, AL080124, AF125949, AL117457, AL133606, AF113689, Y11254, AL110221, AL096744, AL050138, AF113013, AF158248, AL133565, AL122123, E03348, AL137283, AL133080, AL133016, AL050108, Y11587, AF090901, AF113677, AL133093, AF090900, AL049452, AL080137, AL137527, AL050393, AL137550, A93016, AF113699, I49625, AL133557, AF090903, AF090896, AL122093, U91329, E07361, AF118064, AF118070, AL049314, AL137459, AR059958, AF146568, AL110225, U42766, X82434, AR011880, AL049466, AF125948, AF113694, X63574, AF090943, AJ000937, AJ242859, L31396, AL050146, L31397, AF091084, A65341, AL133560, AL049300, AL049938, AF177401, AL117394, AL049382, E02349, E07108, AJ238278, AF017437, A08910, AF183393, AL049464, AL117585, AL122098, AF097996, A08912, AL117583, AF118094, AL049430, AL050024, AL137271, U00763, X70685, AF067728, A58524, A58523, A08909, AL117435, Z82022, X96540, AL133113, A77033, A77035, AL137463, A03736, U80742, AL12297, AL137648, AL133072, AL133014, I03321, AF087943, U72620, I33392, AL122110, X72889, X93495, U35846, AL049283, U67958, I42402, AL137538, AL050172, I09360, AL080127, X65873, Z72491, AL080159, AL110197, AF079763, AF057300, AF057299, E02221, X98834, A93350, AF026816, E08263, E08264, A08911, AL137523, Y14314, AL137521, AL137560, E15569, AF000145, AL133104, AF111112, I26207, AF061943, AJ012755, AL133568, AL137480, S61953, AL137556, AF095901, AF119337, AL137533, U96683, U68387, AL122049, I66342, AF185576, AC006336, AC006222, Y07905, X53587, Y09972, AR038969, AL133067, AL137526, AL080074, AF051325, I00734, AL133077, AR000496, U39656, AF026124, E00617, E00717, E00778, AL122111, AF153205, AF139986, AL110280, E05822, AC004200, AL122118, AL137476, AR013797, AR038854, IJ7767, AF162270, AJ006417, U49908.
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HOCNE77	308	832202	1 - 291	15 - 305		AW291582, AW295479, AI380340, AI688604, AI660552, AI688540, AW006764, AW296326, AW004785, AA594441, AI700219, AI659950, AA470898, AA522452, AA594533, AI695451, AI581787, AI581803, and AI832419.
HPASB03	309	925360	1 - 553	15 - 567		AC007938.
HPASD70	310	522675	1 - 263	15 - 277		AA376961.
HPKAA65	311	753931	1 - 146	15 - 160		T20096.
HROAF59	312	961784	1 - 449	15 - 463		AA445950, AW044412, N59157, AW265503, H46577, AI538390, AW105475, AW337119, H18977, AW013946, H47012, AA912311, H19495, H51387, AA337340, H19075, AA443347, H46576, H19578, H23911, AA445927, H51386, AC004775, and D86957.
HROAL51	313	526487	1 - 227	15 - 241		AA425922, AA355281, AA482768, AA805846, AA515909, H40374, AA309196, AA828042, AA526342, H70615, AA657918, AC005081, AP000472, AC005089, AC005839, AC004854, U52111, AC012599, AP000352, AC007688, AC005256, AC005971, AL080243, AF207550, AC007878, AP001059, AP000359, AL132712, AC005776, AC007649, AL031650, AL008582, AL121877, AL023579, M33387, AC005940, Z97634, AC004016, AC005074, AL034418, AL096774, AP000302, AC005799, AC009336, AC005669, AP000550, AC006596, and AL121782.
HROAO26	314	531173	1 - 119	15 - 133		
HROAT53	315	669179	1 - 418	15 - 432		
HROAV94	316	963714	1 - 307	15 - 321		
HROBC76	317	880935	1 - 345	15 - 359		AF081497, AF193809, and AF185277.
HROBF58	318	735601	1 - 359	15 - 373		AC007240.
HROBF77	319	677615	1 - 373	15 - 387		



HR0BM06	320	934681	1 - 256	15 - 270	
HR0BQ03	321	867044	1 - 387	15 - 401	
HR0BV96	322	867038	1 - 446	15 - 460	Z98048.
HR0BX40	323	835594	1 - 332	15 - 346	
HR0CE61	324	741263	1 - 327	15 - 341	
HR0DC11	325	966298	1 - 276	15 - 290	
HR0DF69	326	766014	1 - 335	15 - 349	
HR0DH54	327	922899	1 - 446	15 - 460	AW295049, and AL049610.
HR0DJ28	328	685922	1 - 592	15 - 606	C14389, D80522, D80022, D80166, C03092, D81030, D80247, AA514186, D80439, AA514188, D80193, C14331, D58283, D59619, D80210, D80240, D59502, D80212, D80043, C06015, D80038, D81026, AW360811, D80157, D80219, D80195, D80391, D80164, D59859, D59787, AA305409, D59467, D51423, D80133, D51799, D59275, D80253, D80045, D80227, C15076, D80258, D80196, D80269, D59610, D80268, D80366, D59927, D80188, D51022, D80248, D50979, D50995, AA305578, C14014, D57483, D45260, D59889, D80024, D80302, D80241, D51103, D80378, AW177440, D80014, AW178893, T11417, H67866, D51759, D80251, AA809122, AW377671, AW375405, D80064, AW352170, F13647, T03116, H67854, D59503, AI525917, C14344, D58246, D81111, AW360817, AW360834, AA514184, C14227, D59317, T03269, AW178906, AI525923, C14973, C14046, D51221, AW179328, T48593, D59474, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, AW378533, AW177731, AW378528, AW178762, AW179019, AW378532, AI525920, AI535686, D58101, C14407, D59551, D80168, AW179020, AW377676, AW352171, AI525227, AI557774, AW178907, AW177733, AW178908, AW179024, D59627, AI525235, AI557751, D51250, AI525215, C16955, AW178914, AW178774, D51213, AI525242, Z33452, AI525912, T02974, AA285331, AW367950, AW177456, AI525925, AW178980, H67858, AW178986, AW179018, D45273, C14077, AW378542, C05763, Z21582, F13796, Z30160, C14298, AW178781, AW178911, AW378543, AW378525, AW378540, AW352163, AW360855, AI525237, D80314, C13958,

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HR0DP45	329	717316	1 - 759	15 - 773	D59859, D80391, D59610, D59787, D80196, D80022, D59467, C14389, D58283, D59275, C14331, D80241, D80043, D51022, D80227, D80253, D80024, D51423, D81026, D50979, D80166, D80195, D50995, D59619, D80210, D51799, D80164, D80240, D59502, D81030, D80251, D51060, D80212, D80188, D80219, D57483, D80366, D59927, C15076, D80038, AA305578, D80269, D59889, AA305409, D80378, AA514186, D80193, C14429, AA514188, D80248, D80522, AW177440, D80045, AW360811, D80439, AW178893, C14014, D80133, T03269, AW375405, D80268, AW179328, AW178907, C75259, D59373, AW377671, D80247, AW378532, AW360817, D80302, AW352117, AW375406, AW378534, AW179332, AW377672, C05695, AW179023, AW178905, AW178908, AW179012, AW179018, AW179024, AW178762, AW352170, D51759, D51250, AW352171, D80949, AW377676, AW178906, AW177731, D80157, AW179020, AW179019, F13647, AW369651, C14227, D51103, AW177456, AW178980, AW177733, AW378528, T11417, C03092, D45260, D80168, D52291, D51079, H67866, AW178914, AW378525, C14407, D81111, AW178774, AW178911, AW378543, AW352163, C06015, T48593, AW177728, T02974, C14344, D58246, D80014, H67854, D59627, AA285331, AA809122, AW178781, AW360834, D59653, C14973, AW378540, D80258, AA514184, Z21582,

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HR0DV70	330	841930	1 - 600	15 - 614	
HR0DX50	331	722502	1 - 159	15 - 173	
HR0EA83	332	710615	1 - 285	15 - 299	AA569577.
HR0EB10	333	963706	1 - 280	15 - 294	AC002540.
HSGSC41	334	576407	1 - 502	15 - 516	AA887982, and AL096803.
HSIAL23	335	508122	1 - 252	15 - 266	
HSICN48	336	524767	1 - 290	15 - 304	
HSICO48	337	529162	1 - 69	15 - 83	
HSICP51	338	531307	1 - 240	15 - 254	AI269973, AW410346, and AB001523.
HSICR32	339	507173	1 - 226	15 - 240	
HSICR69	340	531061	1 - 354	15 - 368	
HSICU08	341	960072	1 - 225	15 - 239	
HSICV54	342	575344	1 - 445	15 - 459	AC005231, AC003108, AP000500, AL049569, AC004491, AC008079, AP000065, AB022785, AC007688, AL035587, AC006211, and AC005015.
HSICV78	343	712629	1 - 356	15 - 370	AW402031, AA363604, AI003250, AA351219, AI905092,

HSICX21	344	531267	1 - 364	15 - 378	AI752702; AA182508, AA045884, T31641, and AF195417.
HSICY35	345	713308	1 - 298	15 - 312	
HSIDA42	346	531264	1 - 200	15 - 214	
HSIDD83	347	531260	1 - 453	15 - 467	AA487103, and R67247.
HSIDG40	348	531071	1 - 298	15 - 312	AI074707.
HSIDH73	349	531293	1 - 302	15 - 316	AC006312.
HSIDJ20	350	526993	1 - 322	15 - 336	AA401843, and AC005041.
HSIDK12	351	531255	1 - 300	15 - 314	Z56029.
HSIDO23	352	526974	1 - 339	15 - 353	AA095552, and AC004098.
HSIDP49	353	531064	1 - 154	15 - 168	
HSIDS36	354	531251	1 - 383	15 - 397	
HSIDT29	355	522341	1 - 316	15 - 330	W27836, and AI046905.
HSIDT51	356	874598	1 - 355	15 - 369	
HSIDV27	357	531246	1 - 305	15 - 319	
HSIDV70	358	925083	1 - 292	15 - 306	
HSIDV75	359	531265	1 - 268	15 - 282	AC008040.
HSIDV82	360	531297	1 - 276	15 - 290	H66107, and H66092.
HSIDW39	361	775139	1 - 507	15 - 521	AI796110, T83017, AI796175, AW242457, AI433547, H60622, and U50545.
HSIDX79	362	712026	1 - 404	15 - 418	
HSIDZ20	363	920867	1 - 99	15 - 113	AA311162, AA295616, and AA332603.
HSIEE78	364	904664	1 - 1374	15 - 1388	D80195, D59859, D59502, D59619, D80227, D80210, D80240, D58283, D80219, D80166, D80269, D80193, D80212, C15076, D80391, D80164, D59275, D51423, D51799, D80253, D80043, D81030, D80022, D80038, D80196, D80188, D57483, D59889, D59927, D80045, D50979, D59787, D59610, D80366, D50995, D80378, AA305409, C14429, D80024, D80241, C14389, C14331, D59467, D80949, D81026, T03269, D51060, C14014, C75259, AW178893, D80134, D51250, F13647, D80268, D51022, AW179328, AW177440, AA305578, D59695, AW178775, D58253, D80168, AW378532, D81111, D80522, C14227, D51079, Z21582, AW352158, AA514188, AW369651, D52291, D80251, AI910186, AI905856, D80439, D80248, AW178762,

AA514186, C14298, AW177501, AW177511, D80064, D80133, AW360811, D51097, C05695, AA285331, AW352117, C14407, AW176467, AW375405, AW378540, AW377671, AW360834, D80302, AW366296, AW360844, AW360817, AW375406, D80132, AW378534, AW179332, AW377672, AW179023, AW178905, AW179220, AW377676, AW352171, AW178906, AW352170, AW177731, D59373, D80247, AW178907, AW179019, AW179024, AI557751, T03116, AW177505, AW360841, AW179020, AW178909, AW177456, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, D51103, D80014, AW352174, AW179004, AW179012, D58246, D80157, AW178914, AW378525, T11417, AW177722, AW177728, AW367967, C06015, AW179009, D51759, AW178774, AW178911, AW378543, AW352163, D80258, D59503, AW178983, AW352120, D59627, AW178781, T48593, C14077, D59653, T02974, AI557774, AI535686, AW177723, D58101, D51213, AW378539, AI525923, D45260, AW177508, AI535850, AW367950, AA809122, C14975, C03092, H67854, AW378533, H67866, D45273, D59317, AW177497, AW178986, AW177734, D80228, D59551, AI525917, D51221, C14973, C14344, D59474, AI525920, D60010, AA514184, D60214, AI525227, AI525925, C14957, C14046, AI525242, AA033512, AI525235, T03048, AI525912, AW378542, C16955, D31458, AI525215, C05763, Z33452, AI525237, A84916, AI132110, A62300, A62298, X67155, Y17188, AR018138, A67220, D89785, A78862, D26022, A25909, D34614, D88547, X82626, AR025207, AF058696, AR008278, AB028859, I82448, AB012117, Y12724, X68127, A85396, AR066482, A82595, A44171, A85477, AR060385, I19525, A86792, X93549, AB002449, U87250, A94995, AR008443, AR016808, I50126, I50132, I50128, I50133, AR066488, AR016514, AR060138, AF135125, A45456, A26615, AR052274, I14842, Y09669, A43192, A43190, AR038669, AR066487, AR066490, A30438, D88507, AR054175, I18367, D50010, Y17187, AB033111, A63261, AR064240, AR008277, AR008281, AR008408,					
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HSIEH45	365	531294	1 - 334	15 - 348		
HSIEH84	366	531300	1 - 140	15 - 154		AC005684, and AC004601.
HSIEO17	367	922867	1 - 1872	15 - 1886		AW381277, AW381279, T62593, AW245141, AW381280, AA827171, AW418543, AI868951, H49462, AA211485, AA579574, AW381263, AI566968, AA568661, AI078750, AA604128, AA019517, AA565823, AA644513, AI188982, T31504, Z42997, AA767424, T89930, H49463, AI948620, H97012, F22114, AI369641, AW381575, AI283644, T87152, AA748475, AA322268, H75949, AA005034, R02581, AI014302, T87057, AI961134, AI379281, T83607, AA322497, AA576177, R27657, N73865, AI254734, AA026869, AI473328, N67589, AA348159, AA129383, T83782, AA953618, H67997, AW381555, AA004420, AA007691, AW149142, AW008764, AI114471, AA425564, AW150911, Z39829, AA814308, AW383774, AW383777, AA333601, AI057250, AA004558, AA004484, AF155114, AL137520, AF176704, AL031178, and AF174597.
HSIEO62	368	531249	1 - 350	15 - 364		AC005575.
HSIFA06	369	866573	1 - 322	15 - 336		
HSIFA29	370	690277	1 - 337	15 - 351		AC005670.
HSIFC65	371	733694	1 - 321	15 - 335		AA315281, and H29636.
HSIFE08	372	839907	1 - 707	15 - 721		AA160422, AC002992, and AC005295.
HSIFE23	373	675419	1 - 423	15 - 437		AC005666.
HSIFE28	374	686056	1 - 301	15 - 315		
HSIFE46	375	718731	1 - 395	15 - 409		R35280.
HSIFH48	376	721310	1 - 436	15 - 450		AI651548, and R55423.
HSIFN66	377	742966	1 - 197	15 - 211		AA577787.
HSIFP22	378	674018	1 - 370	15 - 384		AL135254, AB011096, and AC002094.
HSIFR56	379	733024	1 - 406	15 - 420		AC004537.
HSIFS23	380	919109	1 - 287	15 - 301		
HSIFV95	381	836996	1 - 500	15 - 514		AA190789, AW419467, AA307361, FI1811, Z43375, and

HSIFW89	382	771820	1 - 294	15 - 308	AB018289.
HSIFW94	383	765203	1 - 386	15 - 400	AF060568, and AC001234.
HSIFX92	384	968352	1 - 250	15 - 264	AC005084.
HSIFZ21	385	670415	1 - 372	15 - 386	AA077494, and AC004983.
HSIFZ51	386	919096	1 - 258	15 - 272	D44645, and Z68280.
HSIGA08	387	866568	1 - 307	15 - 321	
HSIGA28	388	686047	1 - 260	15 - 274	AA078252, AC004893, AF076974, and AF110377.
HSIGA33	389	701963	1 - 302	15 - 316	
HSIGD07	390	952508	1 - 311	15 - 325	
HSIGD94	391	961040	1 - 219	15 - 233	
HSIGF11	392	866552	1 - 423	15 - 437	
HSIGG58	393	735682	1 - 422	15 - 436	AA977598.
HSIGG95	394	795631	1 - 333	15 - 347	
HSIGH52	395	726384	1 - 237	15 - 251	
HSIGJ45	396	718728	1 - 345	15 - 359	
HSIGL56	397	906942	1 - 584	15 - 598	AA633962, AI821281, AA574402, and AA573653.
HSIGL94	398	769754	1 - 167	15 - 181	
HSIGM43	399	716259	1 - 514	15 - 528	
HSIGM67	400	751278	1 - 421	15 - 435	
HSIGO07	401	893712	1 - 308	15 - 322	
HSIGO67	402	751262	1 - 394	15 - 408	
HSOAT94	403	537505	1 - 138	15 - 152	
HSOAW33	404	702709	1 - 372	15 - 386	
HSOAW39	405	866228	1 - 221	15 - 235	
HSOBF59	406	738861	1 - 297	15 - 311	H79007, AC005233, AL022476, AC007114, AC007262, and AC005488.
HSOBF65	407	747484	1 - 340	15 - 354	AA749152, AI915081, AA482928, F31867, F31811, AA018923, R70883, Z23147, AI653783, AA862029, W96277, AA775205, AA012829, AI185394, N73060, AA664126, AW089950, AA020873, AA303049, AA579427, AW372037, H91062, AA523695, AI567391, AI674290, AW265688, AA324918, AA568314, AW419389, AA632765, AI619994, T94072, H68343, AA936718, AA579281, AA768179, AI471467, AA568204,

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HSOBL03	408	923317	1 - 276	15 - 290	
HSOBL58	409	735589	1 - 309	15 - 323	
HSOBL59	410	738858	1 - 142	15 - 156	
HSOBL77	411	771729	1 - 503	15 - 517	C06015, D80391, D59787, D80196, D80038, D80193, D80022,

D51022, D80253, D80268, D58283, D51423, C14331, D80247, D80043, C14389, D80366, D80157, D80522, D80439, D59859, D80212, D59275, D80166, D80195, D59467, D59619, D80210, D51799, D80164, D80240, D80227, D59502, AA305409, D80045, D81030, T11417, D81026, D80269, D80188, D80248, D50979, D80219, D50995, D80302, D59610, D57483, D59927, AA305578, C15076, C14014, D80024, D51060, D59889, H67866, D80133, D80251, C14227, AA514186, AA514188, AW360811, D51103, D80378, C14429, AW177440, D45260, D80241, D59653, D51759, AW178893, H67854, C03092, D80258, T03116, AW377671, AW375405, T03269, D81111, C75259, D58246, D59503, AA809122, D80014, C14973, C05695, AW366296, AW178906, D80064, AW360844, AW360817, AI525923, F13647, D58101, AW179328, T48593, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, AW177731, D59474, AW378528, AW178762, AW179019, C14344, D59373, AW378532, AW360834, AA514184, AI525917, C14407, AW378539, D59317, AW177501, AW177505, AW177511, AW378533, AW352170, D60010, AW179020, D51221, D59551, AW377676, AW352171, T02974, AW179024, AI525235, AW178907, AW177733, AW178908, AI525920, C14046, AI535686, D80168, D51250, AW360841, AW352120, AI525227, C14957, AI557751, AW178775, AW367950, AW178909, C16955, D60214, AW177456, AW179004, AW179329, AW179018, AW178980, AI557774, AW178986, Z33452, AW178914, AW178774, AW178754, AW176467, AW352158, H67858, AW352117, D45273, AI525222, C14298, AI525242, D59627, AI525912, Z21582, AW177734, AA285331, AI525925, AW179009, AW179012, AI525215, AW178911, AW378543, AW378525, D51213, AW378540, AW177722, AW352163, C05763, AW378542, AW177728, AW178781, C14077, D51053, T02868, AW360855, AW369651, D51079, AI525237, D59695, D52291, D80949, Z30160, C13958, C04682, D50981, AA305720, D51231, D31458, AI525228, N66429, AI910186, AI525928, D80314, AI525216, T03048, AI525238, AI525239, A62300,					
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HSOBQ06	412	934666	1 - 394	15 - 408	
HSOBQ14	413	719796	1 - 524	15 - 538	
HSOBQ82	414	779093	1 - 312	15 - 326	
HSOBZ60	415	739915	1 - 196	15 - 210	
HSODB93	416	785711	1 - 539	15 - 553	
HSODO56	417	835876	1 - 241	15 - 255	AW162986.
HSODT01	418	915544	1 - 410	15 - 424	U91327.
HSODZ10	419	963671	1 - 356	15 - 370	AC007685, Z85987, and AP000961.
HSODZ58	420	731545	1 - 604	15 - 618	W88862, W88757, N71557, AA025083, AA634227, AA319218, AA501600, AA077817, AI830390, AA715609, AI707788, AI216799, R89436, AA747480, F12535, AA558697, AA747276, AW440810, AC005412, AP000555, AC004034, AP000359, AC000379, AI021918, AF055066, X54156, U94788, AC002312, AC006030, AI034549, AP001037, AI031685, AI049759, AP000553, AC004620, AI117344, AC004895, U95740, AC008372, AC004647, AI022316, AC002565, AC004134, Z82244, AI035413, AP000356, AC006001, AC007193, Z60589, AC009516, AC000052, AC005696, AC005971, AC006254, AI035681, AC004019, AC005250, Z97054, AC002559, AI034429, AI049569, AC005212, AI080243, AC004941, L78810, AI049636, AI135744, AC002352, AC005632, AI008629, AC006255, AC006441, AI132987, AC004866, AI031311, AI031589, AC004000, AC005081, AC005690, AC009501, AC007688, AC002350, AP000967, AC005527,

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HSEOC07	421	952397	1 - 323	15 - 337		
HSPAF44	422	761986	1 - 536	15 - 550		
HSPAK46	423	968901	1 - 426	15 - 440		
HSPAL44	424	754600	1 - 284	15 - 298		AI024323, and AI687282.
HSPAM95	425	918857	1 - 107	15 - 121		
HSPAP89	426	775813	1 - 546	15 - 560		
HSPAQ91	427	789887	1 - 469	15 - 483		AI141763, W22527, and AC005962.
HSPBG79	428	771630	1 - 461	15 - 475		AC006032, and AL133512.
HSPBL63	429	727687	1 - 915	15 - 929		
HSPBM18	430	786056	1 - 724	15 - 738		
HSPME73	431	915722	1 - 1227	15 - 1241		AW377298, AW377335, AW377370, AW377300, AW377374, AW367852, AW377257, AI922500, AW377264, AA927738, HI1886, AI970471, W69888, T81701, AA576526, AW406239, AI199486, AA989195, AW377389, AI123218, AI091150, AA922738, W69567, AW418802, R16877, AI560660, AI612820, AA807380, AA991853, R71372, AA468875, T81488, HI1524, AI538103, AW367837, AW377365, AA742404, AI084549, AJ131890, AF161019, AF176099, AJ131889, and AC003694.
HSPMG03	432	920267	1 - 615	15 - 629		
HTNTD72	433	870030	1 - 556	15 - 570		AI653992, and AA640885.
HTPAA30	434	509812	1 - 169	15 - 183		AA294989, and AA385977.
HTPAC06	435	960791	1 - 352	15 - 366		AA386049, and AC005099.
HTPAF01	436	961063	1 - 333	15 - 347		AA386101.
HTPAG78	437	773936	1 - 374	15 - 388		AA294887.
HTPBH46	438	522888	1 - 300	15 - 314		AA295670, and AA295753.

HTPBQ47	439	922777	1 - 430	15 - 444	AA746310, W20421, R87627, N24299, H43805, AI139901, R92659, AI817040, and AA743934.
HTPBT55	440	509264	1 - 290	15 - 304	AA295440.
HTPCD84	441	783263	1 - 77	15 - 91	
HTPCCK55	442	732458	1 - 129	15 - 143	AA481290, and AB020867.
HTPCN85	443	529760	1 - 207	15 - 221	
HTPCO32	444	973306	1 - 455	15 - 469	
HTPCR51	445	526406	1 - 253	15 - 267	AA294864.
HTPCS70	446	529766	1 - 353	15 - 367	
HTPCT55	447	592481	1 - 330	15 - 344	AC005844.
HTPCT67	448	573704	1 - 338	15 - 352	R20786, AA947456, and AC006356.
HTPCT82	449	869886	1 - 352	15 - 366	
HTPCV62	450	573698	1 - 383	15 - 397	
HTPCV73	451	573686	1 - 371	15 - 385	
HTPCW69	452	935946	1 - 360	15 - 374	
HTPCZ07	453	953769	1 - 129	15 - 143	
HTPD116	454	830553	1 - 199	15 - 213	
HTPDJ03	455	924789	1 - 499	15 - 513	AA150807, AW341449, and AF110184.
HTPDJ94	456	669158	1 - 365	15 - 379	W51842, AW274826, AA410499, AA455588, AW237158, AA220243, AA503778, AA399512, AI925610, AW015854, AW014435, AI081239, AI688411, AI921582, H68676, and AD000671.
HTPDK32	457	699457	1 - 274	15 - 288	AW293772, AW293513, N71206, N22003, AI613520, AA651939, and F04456.
HTPDS34	458	526416	1 - 392	15 - 406	AA386113, AA992843, and AL031053.
HTPDS85	459	541837	1 - 111	15 - 125	AI469516, AA640006, AI560514, AI310606, AL043326, AW409630, AI249946, AI474093, AL049053, AI568060, AA617645, AI419894, AI559752, AI798359, AI962906, AI698491, AI538850, AI349814, AI452857, AL040100, AI702065, AW104767, AW411351, AW079656, AA806181, AI035847, AI252789, AI267282, AI611215, AI335363, AW090225, AI570389, AI343748, AA574323, AW129592, AI597748, AW020932, AI208112, AI680442, AA808311, AI433198, AI635813, AA768725, AI866078, AI654137, F34677,

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HTPDT70	460	573727	1 - 298	15 - 312	
HTPDU59	461	973279	1 - 438	15 - 452	AW193472.
HTPDV73	462	912947	1 - 738	15 - 752	AA280368, AA278898, AA459431, Z78022, and AL049685.
HTPDW56	463	573706	1 - 87	15 - 101	
HTPDW62	464	965356	1 - 442	15 - 456	AA564423, and D14480.
HTPDZ94	465	660751	1 - 329	15 - 343	AA386054, AA100947, AA805935, F07271, AA491106, AA513876, AI962961, R18747, W24282, AA005348, AA705196, AA827410, AA631773, AW452742, AA650378, T70092, AC007877, AC003035, AC005250, AB014088, L11910, AC004190, AP000516, AL008710, AC002487, AL022401, AP000962, Z95325, AC007312, AC003083, AL121654, AP000069, AL023876, AC007751, AJ010395, AL078600, AP000360, AF017732, AC000053, AL050309, AL049591, Z82216, AC004865, Z82203, AC002060, AF121948, Z70041, AL022575, U40455, AC006314, AF128893, AL132800, AC004800, AC006054, AC005061, AL049545, AC006042, AC006379, AL031387, AC005833, AF036938, U82696, AL020989, AL035552, AC005144, AP000493, AL034410, AL049843, AL035067, AC005229, AL136297, AL122023, AL031985, AL117354, AC008498, Z82170, AL033397, AC003001, AC002357, Z98746, Z84719, AL109620, AC006151, AC004992, U09822, AC004070, U69730, Z69721, AC004890,

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HTPEH20	466	573667	1 - 379	15 - 393		AA393545, and AL117356.
HTPEA05	467	869865	1 - 342	15 - 356		
HTPEF02	468	974295	1 - 342	15 - 356		AL035588.
HTPEF35	469	874323	1 - 392	15 - 406		AW392083, and AA279019.
HTPEF95	470	933120	1 - 450	15 - 464		AA295234.
HTPEFM01	471	914956	1 - 446	15 - 460		
HTPEFM04	472	926728	1 - 510	15 - 524		AC005013.
HTPEFN90	473	926462	1 - 311	15 - 325		AC005035.
HTPEFQ07	474	869785	1 - 371	15 - 385		AA236404, AW249340, AW175870, AA191032, U01062, and D26351.
HTPEFS01	475	914908	1 - 327	15 - 341		
HTPEFW04	476	926537	1 - 426	15 - 440		AC005214, and Z56559.
HTPEFX77	477	961059	1 - 420	15 - 434		AA295074.
HTPEFY31	478	869839	1 - 554	15 - 568		AW364673, AW364675, AA837627, AI039309, AI498381, and F23225.
HTPEFY43	479	869844	1 - 581	15 - 595		AA292418.
HTPEFY73	480	906905	1 - 591	15 - 605		AA563747, AA295109, AA295211, AI205010, AL038498, AW104793, AI889566, AI499301, AI298061, C18550, AI829233, AA662740, AW162288, H09744, F12561, AI431434, AL078593, U95742, AC004690, AP000503, AL133245, AF088219, AC005519, AL033521, AL033377, AC006459, AC005875, AL133445, AL049795, AP000555, Z78022, AC007225, U62317, AC004675, AC008989, AL021877, Z86061, AL022316, AC007216, AC006277, AC000134, AC007023, AC005279, and AP000117.
HTPEFZ03	481	922755	1 - 413	15 - 427		R96427, AA582746, AA488903, AA411590, AA091982, AA856817, AW085790, N63755, T83057, AA579188, AA487720, AA363003, AI676249, AA553535, AC004967, AC007225, AC002077, AC005778, AL031680, AC005409, AC005082, AF134576, AC002563, AC006480, AC005348, AC005746,

HTPGD19	482	869842	1 - 543	15 - 557	AC006084, AL022311, AC007278, AC005225, AC004820, AC004126, AC004890, AL031589, AC004263, AF196969, AL031005, AC007774, AC002477, AC008044, AL034400, AP000689, AC005839, AF141309, AL049829, AC006255, AC004223, AC005015, AC007227, AB003151, AF001550, AC004491, Z85986, AC005726, AC000353, Z99714, AF001549, AC007421, AF053356, AC005004, AC005049, AL096701, AL022326, AL021453, AL133445, AC010205, AC001228, AP000553, AF045555, AC002378, AL121603, AC005940, AL031118, AL031295, AC006130, AC005971, AC008071, AL079304, AC007253, AP000116, AP000049, AP000503, AC005722, AC004012, AC004408, Z95116, AL034420, AC006237, Z93017, AC005996, AP000311, AL022313, U80017, L78810, AC000025, AL034423, AL022724, AL031848, AC005780, AC005527, AF111168, AL133241, AL034429, AC002352, AC004477, AL033527, AC005014, AL035405, AC004560, AC005081, AC002492, AF134726, AC003982, Z83840, AC004531, AC004228, AC005484, and AC004400.
HTPGE28	483	974302	1 - 622	15 - 636	AL031730, AL049847, and AL049846.
HTPGF79	484	974301	1 - 447	15 - 461	
HTPGG12	485	969538	1 - 527	15 - 541	AA295087, T82270, AA325128, and AC008013.
HTPGK10	486	963169	1 - 325	15 - 339	
HTPGL49	487	974015	1 - 379	15 - 393	
HTPGR61	488	869802	1 - 303	15 - 317	W19793, AA359208, D31508, AW027675, AI926840, AA961052, AI872593, and AI187329.
HTPGW12	489	969522	1 - 398	15 - 412	
HTPHD53	490	869795	1 - 419	15 - 433	
HTPHE36	491	869814	1 - 587	15 - 601	AL035086, AF053356, and AL049694.
HTPHG90	492	914955	1 - 519	15 - 533	AC005189.
HTPHI08	493	958077	1 - 342	15 - 356	AA295500, AL008734, AL109807, AB026899, AP000500, M29874, AC023172, and AC004617.
HTPHK06	494	975310	1 - 517	15 - 531	AI821881, AI821918, AA338904, AW277171, AI469599, AA501906, AA838190, AI560085, AI932599, AI254913,



AI431434, AW069227, AL038606, AA503600, AI908575, AI524360, AW192065, N46286, AA468022, AA527209, AI278972, AI017251, AI338350, AI631119, AA666332, AW166611, AI002941, AI580250, AI571656, AI002744, AW020599, AI382825, AA302973, AI696595, AA515907, AI537020, AA491681, AI345157, AI305766, AA535216, AA634786, AI284640, AA826671, AI783494, AA507912, AI460009, AL037632, AA188664, AW270619, AA297666, AA639155, AI754653, AI859946, AA487726, AI619436, AA491650, AL038607, AA515048, AA503258, AI634187, F00135, AA526339, AI138329, AI280504, AA484373, AI591375, AL035683, AC003958, Z83845, AI121825, AI049631, AL035685, AC004649, U89337, AC005578, AL049776, AL031680, AC005800, AL109627, AF111167, AL008718, AC005808, Z83846, AC007182, AC004526, AC002492, AC005562, AC004408, AL022333, AI132777, AI109754, AL023279, AL035400, AC004554, AC006142, L78810, AC006271, AC004560, AI079295, AI031293, AC008372, U52112, AC005280, AC007566, AI034429, AC007773, AF196779, Z82198, AL050348, AC002527, AC004000, AC004386, AC002091, U18396, AL022239, AC003043, AP000556, AP000552, AC007057, AC006080, AC022517, AL031186, AC008033, AL031427, AC006356, AC007030, AC004967, Z85996, AL022165, AC006449, AC004659, AC004491, AC004889, AL031053, AC005822, AL035420, AL031736, AC002418, AC011331, AD001527, AC004638, AC018633, AC007263, AL031279, AI009181, AC007792, AC004126, AC005399, AC005411, AC008163, AL022320, Z83851, J00083, AC004634, AC004755, AL022336, AC005668, AC003982, AC005538, AL031283, AI049867, AC007630, U91321, AC003071, AC003664, AC004019, AC012599, AL020996, AC005291, AC002563, AJ006216, AC005839, AC002073, AC002425, AC007227, AC002325, AI035697, AC006236, AC005181, AC005355, AC005480, Z86062, AC006313, AC005484, AC009516, AL031003, Z81313,					
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HTPHR76	495	869791	1 - 1028	15 - 1042	AI075178, AA331929, R55412, AA233754, AA315432, and AA233753.
HTPHS37	496	960637	1 - 324	15 - 338	
HTPHT28	497	952088	1 - 448	15 - 462	AI859675.
HTPHV17	498	926455	1 - 262	15 - 276	
HTPIC25	499	975319	1 - 560	15 - 574	D80268, D80212, D80157, and AC005146.
HTPJE48	500	911422	1 - 300	15 - 314	AC005954.
HUFAA81	501	777951	1 - 430	15 - 444	AI792377, AI860747, AA668905, AA719433, T59285, AI188382, AI926089, F32213, AW009653, AA827383, AA747977, AI754105, AI755214, AA077247, AI754567, AI271762, H73550, AL046519, AA811954, AI687972, AW151870, AA420723,

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HUFAC65	502	750264	1 - 371	15 - 385	AL133640.
HUFAG81	503	966223	1 - 619	15 - 633	
HUFAJ29	504	690591	1 - 428	15 - 442	
HUFAL90	505	788868	1 - 116	15 - 130	
HUFAN64	506	678677	1 - 383	15 - 397	
HUFAP02	507	919805	1 - 455	15 - 469	AI933645, and AF153821.
HUFAU25	508	678024	1 - 424	15 - 438	AA121153, AI678550, R96565, AA433828, AI651396, AI653046, AW362668, AI917104, AI653259, AI339183, and AC009721.
HUFBA27	509	966256	1 - 653	15 - 667	
HUFBN27	510	868997	1 - 388	15 - 402	AL037024, AI132389, AA808742, AA360846, AA666254, F01992, AA689351, H92729, AA360127, C05714, AW270329, N57969, F27846, AI682665, AI382324, AI926183, H64988, AW079664, AA947269, AI814739, AA603530, AI865807,

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HUFBU14	511	868993	1 - 457	15 - 471	
HUFBU41	512	712256	1 - 485	15 - 499	AA731833, and Z85996.
HUFBU61	513	741770	1 - 361	15 - 375	
HUFBV27	514	683030	1 - 521	15 - 535	AW173065, AI216330, AC005829, AC005332, Z82195, and AC004694.
HUFDB55	515	950430	1 - 2157	15 - 2171	AI732436, AA579242, AI954628, AI763064, AA053424, AI493412, AW134526, AA534814, AI967966, AA053043, AI992267, AI342785, AI304542, AI913775, AI864467, AI733752, AW376406, AL134524, AI142134, AL038983, AL037727, AL039643, AL041347, AL039432, AL037443, AL037343, AL037335, AL037436, AL037323, AL049018, AL038838, AL041238, AL047012, AL044125, AL047170, AL040463, AL047219, AL044162, AL040193, AL040621, AL043538, AL047183, AL043496, AL040464, AL041324, AL045817, AL041098, AL040119, AL037435, AL041133, AL044186, AL041096, AL038822, AL040625, AL038532, AL040322, AL041163, AL038761, AL047057, AL040075, AL040617, AL040510, AL044037, AL040149, AL041358, AL041296, AL043467, AL041346, AL041086, AL045684, AL041197, AL041752, AL041246, AL040576, AL043923, AL043814, AL043677, AL041635, AL040839, AL043845, AL041233, AL040294, AL045753, AL043492, AL041602, AL040553, AL046442, AL044064, AL041459, AL044074, AL040472, AL041577, AL040444, AL041292, AL040052, AL041730, AL041523, AL043627, AL041277, AL041159, AL041374, AL041955, AL046850, AL040768, AL040155, AL043848, AL043570, AL042135, AL046994, AL046914, AL045328, AL041142, AL039316, AL046392, AL044272, AL045671, AL045989, AL041168, AA327091, AL045920,

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HUFCH78	516	659722	1 - 508	15 - 522	AA016040, AI457214, AI815197, AW080795, AI963562, AI921206, W22418, AI635935, AF040639, AL035413, AF026947, and Y16675.
HUVDJ10	517	886207	1 - 2009	15 - 2023	AA426634, AA127735, AA424855, AA121510, AI110760, AL079812, AL046457, AA680243, AL121235, AA806796, T63501, AW440545, AI732120, AA453558, AL138265, AI284640, AL079869, AA846568, AI679782, AI313166, AL119331, AW088846, AL046409, AA569648, AL043009, AL037050, AW276817, AA373672, AI805363, AW081165, AW303196, AA521323, AW301350, AA521399, AI431303, H71429, AI270117, AI307608, AI708009, AI986165, AW023672, AW274349, AA490183, AI016704, AW193265, AI610920, AA744021, AW072923, AA577824, AI565581, AW102811, AW265170, AL041690, AI963770, AA640277, AI129446, AW407578, AA581903, AL041013, AW265393, AI564496,

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HVAAE01	518	915732	1 - 515	15 - 529	AI819354, AI560690, AI393635, AI580846, AI024796, AI242427, AI393644, AW020098, R40205, AA568464, F08882, AI190763, AA121140, AA059294, H72102, H92545, N74993,

						and AF097994.
HVAAE94	519	968675	1 - 332	15 - 346		AA844907, AA845137, and AA367039.
HVACL61	520	868572	1 - 511	15 - 525		AI122764, AW276493, AI288219, AI401500, and N74545.
HVAEM04	521	940469	1 - 80	15 - 94		
HVAET61	522	965365	1 - 684	15 - 698		AW135375, AA989283, AI914257, AA886747, AI420461, AL047042, AI064830, AL121270, AI436456, AL045500, AW268253, AI500553, AL036396, AI868831, AW117882, AI349772, AL135661, AI349645, AI207510, AW162071, AI815383, AI863014, AW071349, AI433976, AI687376, AL046849, AL120854, AL119049, AL120736, AL036802, AI349614, AI433157, AI580190, AI906328, AW166645, AA613907, AW080838, AI690751, AL119791, AI920968, AI909666, AL119748, AL047763, AI907070, AI969601, AI340582, AL036759, AI349598, AL036146, AI309401, AI251485, AW132121, AI149592, AI909662, AI500077, AI345111, AI624859, AW303152, AA640779, AI679724, AW238730, AI687415, AI608667, AI349256, AI684265, AI567351, AI345860, AI469532, AI907061, AI567632, AI799305, AI568870, AW302965, AI934036, AI343059, AI343112, AI813914, AI560012, AI349933, AL040169, AI220734, AI345744, AI682106, AI969567, AL040243, AI687728, AI521012, AI275175, AI702406, AL036274, AI538716, AI686926, AI673256, AL121365, AW074993, AW103371, AI889703, AA528491, AW089572, AI873731, AI334902, AI440426, AA528822, AL036980, AI312152, AI753683, AI344182, AW087445, AI349937, AI349004, AA603930, AI631107, AI687362, AI818683, AI499393, AI682743, AL036240, AW274192, AI866608, AA938383, AI282655, AI609592, AI690835, AL038605, AW235035, AA585422, AI678302, AI620284, AA572758, AW301409, AI475371, AI857296, AI307466, AI285735, AI3666991, AW071417, AI583316, AI281779, AI907056, AI366549, AI919058, AI597918, AW195957, AI250293, AL038778, AI345735, AI697137, AI499463, AI439087, AW068845, AI635461, AI886532, AI590128, AI758437, AI635942,

AI699857, AI671679, AI281773, AI564719, AI340519, AW169653, AI440239, AA528529, AI696846, AI800433, AI568854, AI446606, AI636456, AI445432, AI498579, AI625079, AI702433, AI048871, AI497733, AI612913, AI25071, AW148320, AI597750, AI540832, AI613017, AI049085, AI249257, AI038779, AI348897, AI610307, AI866780, AI800453, AW301300, AI500659, AI312428, AI525064, AW074869, AI307558, AI045903, AI680113, AI590482, AI874109, AI633419, AI866002, AI952114, AI539771, AI568855, AW268768, AI475134, AI889839, AI628205, AI269696, AI036247, AI499131, AI224992, AI043326, AI687375, AI866887, AI570384, AW167776, AI121014, AI682841, AI800411, AI921379, AI036260, AI811845, AI934035, AI493248, AA523030, AI271786, AI434281, AI862142, AW168591, AI818206, AI610645, AI042753, AA508692, AI492540, AI047041, AI432229, AI609580, AI469811, AW026610, AI811863, AI282281, AW302992, AI282903, AI281762, AI318569, AI580984, AI349226, AI591311, AI754897, AI561254, I48979, AF078844, AI050393, Y11587, AF090900, AI137527, AF090934, AI133016, AI133640, AF118064, S78214, AF113013, AF113691, I31396, I31397, AF118070, AF125949, AF090943, A93016, AI049938, AI050146, AI080060, AI110196, AI117457, AJ242859, AF113690, AF090901, A08916, AF104032, AI133606, AF090903, AI117460, AI049452, AF113694, AC004738, AI110221, S68736, AF113676, I89947, AI122050, AR059958, AF113689, AF106862, AF090896, I89931, AI050149, AI049430, X84990, U42766, A08913, AI096744, AI050108, AI050116, AB019565, AI133075, AI049314, Y16645, AF113677, AI122093, AI049466, AF017152, AF113019, AI137283, AI080137, AR011880, AI050277, AI122123, AI133557, AI133080, AF113699, E03348, I48978, AI080124, AI133093, E07361, X63574, AF097996, AC005992, X82434, AI137557, AI133565, AI122121, AF158248, U91329, AI137459, AI022147,				
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HVAFD06	523	933527	1 - 742	15 - 756	AI904859, AI904856, and AW270009.
HVAHA06	524	933531	1 - 330	15 - 344	AA148771, W44346, T72825, N62122, AA304792, AA005210, and H14135.
HVAME35	525	968676	1 - 1194	15 - 1208	AA844907, AA845137, AA367039, and AA367020.
HVAMW07	526	951733	1 - 453	15 - 467	
HVAND08	527	958443	1 - 364	15 - 378	AA694346, AF181721, AB032980, and AL133043.
HVANR45	528	930308	1 - 593	15 - 607	AA824393, AW004051, AA812593, AL200988, AA845110, AA835130, AA367324, AW290955, AI539772, and AL042508.
HVAOG11	529	966135	1 - 848	15 - 862	N25812, AW392670, AW372827, AL119483, U46349, AL119319, AL119363, AW363220, AW384394, Z99396, AL043029, U46351, AL119355, AL119457, AL119324, AL119443, AL119484, AL119391, AL119444, U46350, U46347, AL119497, AI142137, AL134524, AL119496, AL134528, AL134538, AL119439, U46341, AL042965, U46346, AL119341, AL037205, AL119335, AL134920, AL119522, AL134531, AL042984, AL134518, AL119418, AL119396, AL119399, U46345, AL042970, AL042975, AL042614, AL134542, AL043011, AL043019, AL042544, AL043033, AL042450, AL042542, AL119304, AL043003, AL119464, AL042551, AR060234, A81671, AR066494, AR054110, AB026436, and AR069079.
HVAOK04	530	925932	1 - 477	15 - 491	AI221399, AI471995, AI467898, AI950299, AI095934,

HVAOW86	531	965298	1 - 1034	15 - 1048	AI034059, AI431317, AA662934, AW327457, AA746600, AI128230, AA025525, AI286104, AI742307, AI160162, AI720824, AI809949, AI669783, AI431319, AI150927, R19215, AI244940, AI090194, AI741975, AA028934, AW043889, AA876265, AA860575, AA844331, AI803250, AA876346, AI245572, AI095557, AI480029, AW393929, AI189306, AI992258, AA044743, T55337, AI122798, AA335548, U56654, AA932576, R13183, AI497894, AA668506, AA564849, AI866853, AI432084, AW272239, AW150208, AI572774, AI270663, AA669015, AA044797, AW157607, AA487470, AA194396, AI825990, AA731264, AA768549, AW129224, AW157188, and AL034345.
HVARE86	532	965243	1 - 487	15 - 501	N25431, AI669981, AA809138, AA854642, AW241780, AI636296, N25553, AI768827, AA962150, N34122, AI478713, N34151, R88992, H99894, R68206, R68207, and R86350. AI899955, AI913228, AI066470, W46957, C01207, AI470293, AI247298, AW020397, AI702527, AI886124, AI801793, AI888671, AI249946, AI929108, AI538850, AW084097, AI887620, AI037454, AI925404, AA088789, AW088944, AI110306, AL038529, AL135025, AL045413, AW085350, AI687568, AI623389, AW023338, AW008737, AI590043, AI866082, AW058233, AI873638, AW268261, AI345415, AW104056, AI471429, AW161098, AI537991, AI624956, AI282376, AI624971, AI161278, AI873604, AI687166, AI539847, AW021717, N29277, AI244380, AI539153, AI936003, AI335363, AI539057, AI560679, AI685211, AI913452, AA808175, AW083573, AI887430, AL042488, AI458443, AI890391, AI261589, AI473528, AW082600, AI570264, N57346, AI628325, F27788, AI805598, AW168031, AI473434, AI631216, AI685080, AI473451, AW149227, AI432570, AL079799, AI440284, AI583578, AI355277, AI613449, AI352514, AI344785, AW059713, AI679069, AI541056, AW262983, AI800370, AI916419, AI718513, AI689614, AI500061, AI289791, AI521005, AW051088, AI289310, AA806719, AW104062, AI469516, AL048323, AW160916, AI698391,

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HWGAG91	533	773364	1 - 272	15 - 286			AA689293, and AA804485.
HWGAC19	534	668126	1 - 409	15 - 423			AC006101.
HWGAC45	535	754792	1 - 313	15 - 327			AA262164, N27049, AA491312, AA143186, AA346611, N48382, AA333620, Z28515, T81958, and AB014536.
HWGAE55	536	974955	1 - 484	15 - 498			
HWGQD52	537	726390	1 - 98	15 - 112			AA437169, and AB018307.
HWGQF79	538	882611	1 - 438	15 - 452			
HWLAL74	539	761974	1 - 288	15 - 302			
HWLBI74	540	839518	1 - 422	15 - 436			AL035425.
HWLBJ06	541	934614	1 - 431	15 - 445			AI123402.
HWLBK76	542	731099	1 - 515	15 - 529			AA193193, and AI609548.
HWLBK80	543	933865	1 - 534	15 - 548			D42047.
HWLCV54	544	929742	1 - 443	15 - 457			AL139054.
HWLDO22	545	838721	1 - 434	15 - 448			AI733811, AI640317, AI916600, AA757207, AI732839, AA745673, AI792633, AI264658, and AW196083.
HWLED58	546	830330	1 - 431	15 - 445			
HWLEF86	547	785193	1 - 138	15 - 152			
HWLEH06	548	934649	1 - 542	15 - 556			
HWLEH47	549	709376	1 - 408	15 - 422			
HWLEI16	550	729050	1 - 316	15 - 330			
HWLEJ07	551	952396	1 - 396	15 - 410			AB023217.
HWLEK39	552	918545	1 - 359	15 - 373			AI823397, and AI817711.
HWLEN08	553	958509	1 - 1758	15 - 1772			AI655644, AW327476, AI031969, AI205174, AI188440, AW119015, AW004593, AI863261, AA594110, AI346704, AI090352, AW361848, AW117393, AI148841, AW084108, AW327477, AI613225, AI192097, AA598697, AW130228, AW005953, T80227, AW195717, AA442259, AA883126, AA160298, AA456223, W86369, AA291990, AI360945, AI916226, AA047326, N68259, AI587282, AA831041, AI028392, AA411013, W40265, H94896, AA923081, W86305, W26837, AI680635, AA836337, W40218, AW205315, AA568678, AA781825, AA293214, AI356302, R96627, AA055222,

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HWLEN20	554	963418	1 - 423	15 - 437	
HWLEO59	555	974078	1 - 390	15 - 404	AA773463, AI634187, AA828637, AW069227, AI457313, AW023111, AI216990, AW338035, AW338021, AI791211, AI821947, AA804943, AI753267, AI636341, AI243789, AA630854, AI216151, AI755214, AI754567, AW245354, AA284247, AI493587, AA086318, AI889579, AI554807, AA502532, AA515728, AA757426, AI754105, AA634991, AI356440, AA456924, AI206841, AI884340, AA501461, AW272294, AI249365, AI249688, AI568683, AA225406, R92658, W02749, AI038304, AA775205, AI445216, AW151201, AI537800, AI821382, AI224619, AL042373, AA557911, AI961983, AA535216, AI821931, AI417469, AI569100, AA857812, R34070, AI189682, AA832145, AW192599, AW083678, AI278972, AI199816, AI292236, AA626829, AI205181, AI118925, AA609834, AI049709, H73550, AA573127, AI912401, AI187148, AA491767, AA297195, AI538236, AI042771, AW303872, AI620992, AI799569, AI042906, AW002831, T47138, AA054156, AW151870, AI119838, AC004590, AC005736, AC005225, AC005071, AC005015, AP000114, AC005409, AC004491, AC006312, AD000092, AC007277, AC005778, AC010205, Z83844, AC002511, AC005972, Z83847, AC004686, AI034423, AC007011, AI021453, AI049795, AC007227, AI080243, AI035410, AP000046, AP000553, AC007664, AC004673, AC007371, AC005305, AC005049, AC007040, AC006121,

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HWLEP95	556	751199	1 - 475	15 - 489		
HWLEQ36	557	966250	1 - 437	15 - 451		
HWLEQ81	558	934224	1 - 210	15 - 224		AA625092, and AL022328.
HWLER88	559	915168	1 - 320	15 - 334		
HWLFB08	560	849136	1 - 580	15 - 594		AL133245, AL133243, and Y17267.
HWLFC80	561	830279	1 - 571	15 - 585		
HWLFE50	562	830283	1 - 580	15 - 594		AW085982, AI521525, AI269608, AW020150, AI926102, AW151541, AI537368, AL041375, AI452836, AA484892, AW275432, AA535216, AW117860, AI797998, AI927275, AI755214, AI754567, AA487569, AA302979, AI984168, AI049845, AI754105, AI004591, AI801563, AI587349, AI249688, AI751341, AI884383, AI921706, AA644090, AA456924, AI355246, AA610381, AW003886, R94909, AI753904, AI697235, AA610433, AI434653, AI973173, AA410788, AA086318, AW151247, AI697239, AW021917, AI862716, AI697242, AI568376, AA833896, AA669234, AW104161, AI446623, AA228778, AI141130, AW057760, AA833875, AA703818, AA846923, AI421257, AA761623, AW277174, AI357762, AI291037, AW270768, AI915081, AW083678, AA643441, AC007617, AC007216, U95742, U95739, AC007537, AP000032, AC006511, AC007226, M63543, AC006965, AC006455, AC005288, AC007563, M63544, AC005529, AC012085, AC004020, AC005839, AC006449, AC009516, AP000689, Z85987, AI023575, AI049776, AC007450, AP000350, AC005082, AP000501, AL050307, Z97054, AC006530, AC005971, AC002544, AC005755, AC005231, U91326, AC005911, AL109963, AC007327,

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HWLFF40	563	830287	1 - 286	15 - 300		AC005751.
HWLFF62	564	915155	1 - 437	15 - 451		
HWLFH47	565	719752	1 - 467	15 - 481		Z99396, AW392670, AW372827, AW384394, AW363220, AL119355, AL119341, AL119497, AL119319, AL042551, AL119457, AL119324, AL119396, U46341, AL119443, AL119484, AL119363, AL119391, AL119522, AL119483, AL119335, AL119496, U46351, U46349, AL036418, AL038837, U46346, AL119399, AL134902, U46350, U46347, AL134528, AL037051, AL119444, AL036725, AA631969, AL119418, AL134518, AL042614, AL037205, AL119439, AL042433, AL042984, AL042975, AL036858, AL042965, AL134920, AL119401, U46345, AL134536, AL043008, AL042450, AL134525, AL134538, AI142131, AL039074, AL036924, AL042970, AL042544, AL043019, AL039912, AL043029, AL119488, AL042542, AL038509, AL043003, AL119464, AL037085, AL037094, AL037082, AL037526, AL036196, AL036190, AL037639, AL037077, AL036767, AL038520, AL036268, AL036998, AL038851, AL036733, AL037027, AL037615, A81671, AR060234, AR066494, AR054110, AB026436, AR023813, AR064707, and AR069079.
HWLFJ51	566	853602	1 - 328	15 - 342		
HWLFK50	567	918539	1 - 288	15 - 302		AA131248, and AI288287.
HWLFO70	568	756554	1 - 389	15 - 403		AC005595, U47924, AC005531, AP000347, and AC005754.
HWLFO82	569	779461	1 - 494	15 - 508		
HWLFO92	570	791052	1 - 577	15 - 591		
HWLFP37	571	708985	1 - 598	15 - 612		AI284640, AL046409, AW327868, AA584145, AI754955, AI431303, AI963720, AA490183, AL044858, AL119691, AA507824, AL037683, AW193265, AI334443, AA581903, AA846876, AI270117, AI613280, AI281881, AW265385,

AW303196, AA521399, AA521323, AA623002, AW274349, AA847499, AW301350, AW439558, AI076616, AI350211, AA493708, AW270382, AW021583, AA525824, AI345518, AA584201, AI754658, H71429, AI499938, AL042753, AA533036, AA126450, AA613232, AA984708, AW274346, AA682912, AA719292, AI110770, AA503473, AA502104, AA528516, AA483771, AI110760, AW072923, AL042420, AI568678, AA584167, AA632837, AA631507, AI246119, AI434695, AI732120, AW080811, AI254615, AA394271, AI860013, AI133164, AA613227, AA470969, AA491814, AL038474, AA468131, AA649642, AI610159, AW304584, AI536665, AA572713, AA603835, AI246796, AA720702, AW073470, AI192631, AI589230, AA780515, AI357288, AA177063, AI499503, AA084624, AA469451, AI133297, AI801591, AA531372, AA665199, AI561060, AW103758, AW276827, AL048626, F36273, AI064864, AA494163, AA713891, AA129446, AI312309, AI696955, AI379719, AA602047, AA551503, AA577906, AA806796, AA548058, AA828042, AI624097, AI633390, AI368256, AA552856, AA552843, W79504, AA214342, AW148792, R88888, AI801600, AI564185, AC005529, AC005527, AC007298, AC005694, AC006251, AC006312, AC002476, AC003071, AL121748, AL121603, AC004854, AL022313, AC004686, Z97054, AB020865, AL109967, AC004381, AC004975, AL080243, AP000088, AC004890, AC005837, AC006213, AC005772, AC004650, AC002310, Z68870, AL031286, AL080250, Z97989, AC006960, AL031311, AC004987, AC007919, AL034402, AC008372, Z82976, AC004019, AC002430, AC004859, AC004815, AC002425, AL139054, Z98752, AP000557, AC003108, AC004755, D87675, AC006211, AL049758, AP000555, AC007384, AC016026, AC005412, AC005324, AC005295, AC005751, AC006449, AC001231, AC004076, AL049839, AC003048, AC005531, AP000065, AL009172, AC007899, AC007731, AL121578, AC003983, AC002045, AC005154, AL031584, AC005500, AC005081, AC008115,



AL049869, AC005037, AL031848, AL080242, AC007216, AC010168, AL023575, U47924, AF196971, AP000552, AL021578, AE000658, AC007066, AC007790, AC008079, AP000692, AC007688, AC003664, AC005189, L44140, AC005562, AC004990, AC007285, AC020663, AC004526, U91323, AC002400, AC002059, AL049643, AC000052, U95742, AC007563, AC002549, Z86061, AF111168, AL021453, AC005839, AC002429, AC005944, AC005520, AF165926, AC005914, AC005180, AC006006, AC006450, AC005747, AF001549, AC016830, AB022785, U91321, AC004033, AC006111, AC004796, AL136295, AL049759, AC005535, AC007283, AP000359, U80017, Z93020, AL008719, AC006026, AC004638, AC007032, AL035413, AC006344, AL133245, AL031670, AC008012, AC006486, AC010072, U66059, AC005768, AC007842, AL031577, AL050318, AC009946, AJ010770, L78833, AC005486, AL132985, AP000961, AL121694, AC004933, AC008109, Z98051, AL049776, AC006064, AL049709, AC009399, AC000025, AC003007, AC006160, AC002307, AC007685, AC005695, AL034554, U85195, AL034350, AL049843, AC005300, AC004659, AC004883, AF045555, AC002470, AL035659, AC003692, AF053356, AL031118, AC005696, AC007051, AD000092, AL121825, AC002347, AC008101, AC005632, AC005288, AR036572, U91328, AC003098, AC004522, AC007666, AF134726, AJ003147, AC005924, Z98742, AL096701, AC010202, AC007226, AC007358, AL008630, AC006512, AC004982, AC004972, AC007363, AL031257, AC000066, AL031281, AC004814, AC022517, AF064861, AL021707, AL022302, AC006130, AC004893, AC005988, AC004811, AC009721, AL049699, AP000501, AL121655, AL121653, U62317, AC016831, AL031687, AC005701, AC005740, AC006538, AL121652, AC006120, AC007245, AL117258, AC006088, AC005829, AF190465, AL022238, AC005104, Z99716, AC003025, AL035695, AC002395, AC004865, and Z83844.				
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HWLFP46	572	882848	1 - 610	15 - 624	AA167712, AA484145, AI042311, AI251597, AI816141, AA582528, AI382825, AI732151, AI355426, AA832175, AI041146, AA663600, AI469968, T94249, AC005483, U07563, Z98036, AI031432, AC005089, Z99754, AC006335, AI031678, AC004534, Z98884, U95743, AI022336, AI050313, AC004045, AC003080, AC005037, U16300, AC002301, AC004808, AI022725, AC004890, U52112, AC011311, AI035664, AI023582, AC002425, AC005280, U62317, AC005599, I05724, AR002329, I08174, AI9048, AC005777, Z83820, AI109758, AC008150, AI096799, AB020858, AC004584, AI031848, MI6553, AB007955, AI049553, J02846, AP000310, AB000877, AC004631, Z68870, AC005331, AC004559, AC004237, Z82248, AC005776, AC000087, AC004144, AC006046, AC005775, AP000148, AI096774, AC005031, AC006130, AP000233, AC002369, AC004874, AP000116, AC008116, AC004813, AC004997, Z95116, AC002996, AC007243, AI022313, AC005155, AC005839, AC004999, U80017, AC006364, AF064861, AC002526, AC002563, AC007666, AI009181, AC007388, AC009275, AC006502, AC005585, AC004852, AC007462, AI021368, AC000052, AC008039, AC003101, AC003684, AC007308, and U66059.
HWLFQ48	573	721154	1 - 243	15 - 257	
HWLFS01	574	915531	1 - 453	15 - 467	
HWLFS86	575	830246	1 - 578	15 - 592	
HWLFV61	576	922924	1 - 135	15 - 149	
HWLFW01	577	915527	1 - 516	15 - 530	
HWLGL36	578	806724	1 - 419	15 - 433	
HWLGP10	579	883139	1 - 306	15 - 320	
HWLGP21	580	958259	1 - 129	15 - 143	
HWLGR72	581	958284	1 - 629	15 - 643	
HWLGT12	582	966044	1 - 358	15 - 372	AF047825.
HWLGT54	583	952732	1 - 691	15 - 705	
HWLGV83	584	871680	1 - 600	15 - 614	AA224977.
HWLGX56	585	830329	1 - 570	15 - 584	

HWLHC73	586	830319	1 - 551	15 - 565	
HWLHF49	587	926878	1 - 538	15 - 552	
HWLHO01	588	915158	1 - 514	15 - 528	AI799075.
HWLHP05	589	931087	1 - 404	15 - 418	AW089625, AA577824, AA188940, AI354847, AI679002, AI732911, AA309533, Z23155, AA192366, AI243789, AA829044, F33184, AW084152, W96277, AA825954, AW265688, AI243793, AI287921, AA856815, AA551067, AA640277, AA618453, AA642787, AA371410, D51877, AA764812, AA831913, AI114494, F16409, AI862716, AA385775, AI028498, AI791390, AA569053, AI185394, AA742815, AA226532, AA599080, R67701, AA678472, AI885465, AA654482, AA297969, AW304699, AW419389, AI119331, AI292976, AA601673, AI174531, AA610255, AA878407, AW243945, T49184, AA572987, AA728861, AA558366, AA582746, F26072, N40092, AA493829, AW069227, AI120543, AI345497, AI247973, AW068786, AA578535, AW338506, AI039257, AA513916, AA320105, AI689198, AI008718, AC005071, AP000503, AC004253, AI034417, AC005015, AF134726, AP000031, AC004765, AI133448, AC004019, AI022316, AL049697, AC002432, AI031682, AC005488, AI031056, AL024498, AC016831, AC002565, AC005529, AC004185, AC005081, AF001549, AI022318, AC002425, AP000556, Z98946, AC006146, AC005274, Z99128, AC002381, AC002094, AI133245, AI121748, AC005696, AI133163, AC011331, AI034420, AC005225, AC002312, U91323, Z83845, AC006312, Z83844, AC004531, AC005736, AI049832, AC007308, AC005527, AF196779, AC002550, AC004996, AC006449, AC006356, AI133382, AP000553, Z84487, AC004812, AP000032, AP000509, AC007731, AC005730, AC005264, AC005500, AC006130, AI031390, AC004167, AP000346, AC007055, U78027, AC005011, AI031311, AC004854, AC007057, U91318, AJ246003, AP000557, AC005754, U95742, Z84469, AC005678, Z82198, AC003982, AC005180, AF053356, AC005776, AC004832, AI109798, AP000135, AI050318, AC005486, AC002553,

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HWLHR93	590	952387	1 - 367	15 - 381	
HWLHT06	591	934217	1 - 362	15 - 376	AA507824, AA493708, AW406755, T40452, AA703891, AI365988, AW193265, AI284640, F29989, AI554201, AI431303, AA580808, AI350211, AI613280, AA467820, AW438643,

AI043719, AI583283, AI038705, AI270117, AA577906, AA468244, AI610159, AA602047, AI619997, AI751216, AW270270, AI559251, AI345654, AW072587, AI281881, AA523242, AW148792, AW274346, AI792287, AI037683, AW273218, AI969436, AI962050, AA229814, AA483771, AA491284, AW276827, AI539563, AI334443, AA720702, R35746, AA584167, AI801482, AI754955, AI472222, AA446544, AI537506, AW021583, AI085719, AW303196, AW274349, AA621858, AA649781, AW302450, AL119691, AA653618, AI589461, AI375542, AI282511, AA555141, AI254615, AA552856, AI863054, AI917271, AI439210, AA552843, AA908468, AL041690, AW301350, AI732120, AA533725, AA857486, AI286356, AI625647, AL048925, AA507547, AI702314, AI355206, AI053672, AI634384, AW440545, AI357288, AI046898, AW149339, AI338350, AA847952, AA579366, AA493621, NS3150, AI733755, AI963720, AW238278, AA629992, AI192631, AA856954, AA630925, AA177061, AA551503, AA581903, AA722372, AA490183, AW276435, AW087356, AI696962, AW238542, AW028429, AA653375, AA631507, AI149478, AI251436, AW406447, AI307608, AW008952, AW071196, AA856848, AW408047, AW085780, AA225944, F28204, AA639248, AA513141, AW194250, AI583612, AW088846, AA468022, AW079135, AI568678, AA548058, AI744826, AF034184, AW341900, AA521323, AA092078, AA492166, AA584082, AA610491, AA502104, AA747105, AA586458, AA665330, AW080125, AI046205, AA559290, AI281903, AI954260, AI744995, AA533036, H95681, AA623002, AA521399, AA747276, AI250019, AI860013, AA661948, AA581463, AA470969, AI355224, AA610271, AW327868, AA503473, AI633025, AI624097, AW238583, AA502155, AA482681, AA526758, AA484696, AW419262, X75335, X55930, D83989, M37551, Z79422, U57005, U67827, X54181, X55923, X54178, U18391, U18392, U57006, U18395, U18394, X55925, X54179, U18390, U67829, X55932, X55926, U57009, X55927, U57008, I51997,

AF077058, L47228, X55929, X55933, U18399, U18398, X53550, X54175, U67831, AC004890, AC007676, AC005954, AF015153, U57007, AC005777, U18400, AL117337, X55922, U67825, U18388, M87919, U18387, U67801, U18396, U18389, U67826, U14705, AP000555, AC005726, X54177, AP001037, AC005089, U14701, AC005940, AL021155, Z78627, AL021546, AF176915, AC005378, AF015157, AL109802, AL110505, AC005261, AP000113, AF015156, AF217403, AC005212, AP000556, AC004990, AC005664, AC007051, X74558, AF128525, AF107885, AC007308, AC004686, AC007243, L48038, AP000513, AF015147, AL133246, AL031577, AC005520, AL031257, AF015149, AB023049, AC006312, AL078476, Z83840, AC005231, AC016026, AL034549, AL031281, AC004491, AC007845, AC005538, U91326, AC006116, U57004, AC007421, AL033521, AC003041, AF070718, AF015151, U67235, AC009946, AC009516, AP000432, AC006600, AC004771, U07000, M87925, AC008012, AF205588, AL035681, AL021937, AC005544, AC002430, X78901, AC005015, Z49235, AB000878, AC015853, U11309, AC005844, AC000026, AC004894, AC007384, AP000469, AC007055, AC005944, Z84480, AC002082, AL117354, AC005105, Z97053, AF015150, AL035659, U91322, AL049795, M15205, AC002119, U67231, AC003982, AC007664, Z75744, U62317, U67230, AC005519, AC002059, AL035455, AC004613, AC003104, AL033523, AL109759, AC004895, AC002301, AP000552, AF015148, AC007324, AL022332, AC002054, AC007919, AC007546, AC006023, AC004841, AC009225, AC002559, AC002368, AC010206, AL031368, U67226, AP000567, AC006120, AC004972, U22376, AC005288, AC004600, AL031311, AL050097, AL031672, AC005081, AL049745, AC008498, U67229, AP000553, AL021939, AJ131818, AC005779, AL035071, U67213, Z49237, AC004028, U67234, AL031657, AL022721, AC002470, AC005011, AF015162, AC007371, AL035458, AL096829, AC004595, AL022315, AC007707, AC004531, AL050312, AC005500, AC005757, AC006207,

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HWLHT92	592	830322	1 - 446	15 - 460	Z85996.
HWLIC75	593	830321	1 - 45	15 - 59	
HWLIF03	594	830233	1 - 328	15 - 342	
HWLIH21	595	917551	1 - 803	15 - 817	AI833131, and AI581835.
HWLIJL65	596	747440	1 - 512	15 - 526	AA521246, AA834532, AA664369, AI827922, AA766094, AI458257, AI915368, AI914009, AA740983, AI128279, AI128274, AI160827, AI222682, N30618, AI872758, AI569363, AW020599, AA524229, AA635389, AA847949, AL033527, AC003663, AL109847, AC004551, AC002394, AC007371, AL109963, Z97989, AC002067, AC007057, AL022238, AL024498, AC005412, AC007639, AF196969, AL049760, AC005952, AC002565, AL049776, AC005520, AC005844, AC005553, Z84487, AC002563, AJ011930, AP000493, AC002036, Z93930, U82757, AI050307, AF199339, AC004382, Y13537, Z85994, AC006241, AP000100, AC004805, AL031281, AL031591, AL031276, AF047825, AC006515, AC002554, AC007637, AL049569, AC005781, AC003104, AL031681, AC005722, AC004504, Z98742, AC006141, AL035417, AC005886, AC006512, AC004491, AC004216, AL022721, AL049692, AL031767, AC006057, AC005486, AC007051, AC005081, AC007766, AL109984, AC003098, AC006077, AL035411, AC005940, AC005736, AC007225, AC008967, AL049872, AC005225, AL049794, AP000103, AP000032, AL031283, AP000263, AC004033, AL031295, AC011422, AC006001, AL031120, AC007226, AC002470, AC002990, AL031311, AC004167, AC002350, AP000036, AC005088, Z98750, U47924, AC004655, AC002070, AC005529, U07562, AC006117, Z98044, AC005324, AC004851, AL021154, AL121603, AC002126, AC004016, AP000512, and Z97053.
HWLIN37	597	712654	1 - 190	15 - 204	AW291552, AW138601, AI077575, AA780149, AI470521, AI079239, AI350461, AI190936, AA700035, AA700691,

						AA846411, AI075806, AA745860, AW104705, AI653668, AA620868, AA931634, AI358441, AI022949, AI147873, H78701, AA411234, AA599147, AA705723, AA912904, AI808843, AI400574, H41413, AA526292, AI682941, AA807011, AI027243, W47156, T73150, AA885483, AI300065, AI807760, AI457358, AI866405, AI986123, AF100749, and AR060022.
HWLJO73	598	761965	1 - 309	15 - 323		
HWLJIS13	599	933552	1 - 351	15 - 365		AI474787, AW132088, H26632, AI697470, AI748801, AI985035, AI613073, AA552037, AA486673, AW302255, AW273755, AI654071, AI833092, AA485303, AW001735, AI633999, AA555209, AI889437, AI678144, R54622, AI720421, AA630239, AI709263, AI624856, AI925932, AI720864, AI749272, AI493247, H44026, AA347725, H14641, AI459687, AW270873, AI700126, AW271969, AI433393, AI963703, AA552441, H70926, AW377424, AA838075, AW299847, AW377450, AI678860, AI539136, AW361066, AI470617, AI284215, AW339456, AA553745, AI700750, D25586, AA553746, AI720744, AI916628, AI279141, AI690207, AI735160, AI581560, AI631055, T96160, AI283780, AI707504, AI273946, AI749659, AI832808, AI721199, AW363628, T94910, AI445357, T39321, AI611197, AA953731, AI873587, AI275765, AI275202, AI480124, H24673, AA485460, AI749891, T94865, AA553861, AI687436, AW242695, T24762, AW375718, and AI263070.
HWLJIS62	600	722358	1 - 499	15 - 513		AI335089, AW071975, AI922669, AI343825, AA875852, AI554367, AI290781, AI357884, AI088635, AA972857, AI129815, AI168499, R62969, AA813538, AA702864, H05057, AA436814, R39812, N78991, AA442570, W74268, AA133776, R56602, T48889, AA627735, AA142932, R80928, Z39624, R59136, R66723, AA993978, R67603, F02373, AA228698, R66262, AA368546, AA115592, AA486747, W17367, W79882, AL034397, and AJI32502.
HWLJW68	601	925892	1 - 472	15 - 486		
HWLJB04	602	926066	1 - 446	15 - 460		AA862391, and N62231.
HWLJC30	603	830232	1 - 726	15 - 740		AI767585, AA516447, AW272896, AW299599, AA974871, AA524410, AI963626, AW204624, AI698859, and R67729.



HWLJE89	604	928258	1 - 572	15 - 586	AW270505.
HWLJG57	605	849123	1 - 518	15 - 532	
HWLJL14	606	832205	1 - 338	15 - 352	
HWLJL46	607	830226	1 - 342	15 - 356	
					AA506744, AA219542, AA776548, AA084679, AW248724, W47141, AW249151, AA679173, AA101377, AA668421, AA300049, AI445699, AA147521, AI702049, AI002952, AW265468, AW148821, N78600, AL138262, AW192930, AA757406, AL121039, AA621720, AW410844, AA180857, AI064968, AA172103, AA846014, AW020198, AW247338, AA077619, AA593480, AA182629, AI679759, AA516247, AA778962, AI133083, AI819391, AI283938, AW008184, N53448, AI267356, H94598, AA484651, AI241637, AW243808, AP000353, AL008720, Z92546, AC004150, AC004825, AL121655, AL035451, AL050307, AL133353, Z83308, AC005207, AC007514, Z82249, AL137548, AC004999, AC005031, U80017, AC020663, AC006023, AC006539, AL020997, AC005412, U71148, AL050341, AC006449, Z99755, AC002984, AL023575, AC003086, U62317, AL022313, AL078638, AC006241, AF207550, AC002430, AC002558, AL031295, AL022721, Z97055, AC002418, AC007384, AC004821, Z83820, AC006333, AF124730, AC004234, AC005484, AL021939, AC004386, AL022238, AC006130, AC005231, AL031282, AC002544, AL031668, AL109952, AL078581, AC005519, AC005696, Z98742, AL050129, AC006441, AC005694, AL031680, AL096801, Y18000, AF196779, AC004972, AC004019, AL049758, AP000300, AC003002, AP000045, AP000113, AL035417, Z98941, AC005043, AL031584, AC005874, AF134471, AC007731, AC004765, Z83847, AC005500, AL049776, Z93023, L47234, AL031728, AL135784, AC005377, AL096701, AC007684, Z95114, AC006581, AC003004, AD001527, AL031186, AC004505, AC005911, AC005399, AC009516, AC008009, AC005261, U95742, AC007565, AP000349, AP000230, AP000144, AC002425, AL109967, AC006254, AL022162, and AC007387

HWLJN54	608	729051	1 - 603	15 - 617	T91244, T81477, T80967, AW269968, AI110776, Z95437, U69569, AC004536, AC004855, AB019437, AC009233, AC006986, AC007274, AC006991, and AL031119.
HWLJN66	609	830229	1 - 541	15 - 555	Z97053, AL031005, and AL022326.
HWLJP79	610	963698	1 - 836	15 - 850	AL044649, AW149822, AW372403, AW022126, AI937028, AI832398, H52755, AI902686, AI523476, AI125713, D61865, AA913606, H23922, AI671047, AI523319, AW338626, AW338631, C05054, AW069280, AW025428, AI017617, AI554450, H65437, R83782, AW020014, AW384060, N20088, AI025375, AA358941, AW020227, AW372379, AW193889, AI921185, AI097582, C16388, C16369, AW021585, AI269495, AW118958, C16167, AI018455, AW384059, D54010, AI268738, AA380556, AI219878, H99109, AI278598, AI300002, AA503421, AI796695, AI421622, AW118123, AA708591, H88061, AI242119, H48158, AI925067, AA631826, AW080615, R71561, AI033678, AI423988, AI424104, AI222739, AA213469, H02742, N20549, AA744800, AA434408, D61931, AA179347, AA55272, D61016, AA564521, H04059, H45223, D81374, AI744022, AW151012, AA729594, AA987628, D60574, AI762567, H49945, H02770, H02165, AW242024, AA179154, AI690550, AW262043, AA551955, AA507614, D54275, AA214237, T35691, AA725244, D60843, C15668, AW362248, H02769, T30072, AA419350, AW376397, R80139, T05116, D60575, D60695, D60842, AL048702, H02164, AA527710, AW085223, AW021333, N29664, AA679787, R15695, AA744656, AA622316, AW407259, T18586, AI709204, D58121, T31072, H42460, H89037, C16578, C15955, D55586, AA482734, AW169465, H52797, H88062, AA715156, H88954, AA040056, AW006042, R10801, R63592, AW384124, R21798, AA330605, D52526, AW366348, AW078841, R71506, R10709, R34609, AA405202, AA151219, AI671907, AA040042, AA151218, AW269344, F13646, AI000596, AA861747, H03111, AI869576, AW362494, AA225398, T90939, AI302914, R34216, AA298995, AI355633, AA516073, AA089751, AA405203, R26368, R63540, AL079897, AI748860, AA910712, AA876685, AI648500, AA091600,

HWLJR77	611	883207	1 - 647	15 - 661	AI902685, AW366389, AA383198, and T18524. AI732905, AI833168, AI911154, AW001333, AA828206, AA296957, AW001526, AI749030, AI880265, AI984533, AI984522, AA937899, AW000842, AW001511, AI708091, AA297154, AI989764, AW050874, AA297177, AI673643, AI673652, AA297205, AC002301, and I95747.
HWLJX38	612	925868	1 - 148	15 - 162	
HWLJZ30	613	925870	1 - 596	15 - 610	
HWLKC87	614	956205	1 - 517	15 - 531	AF179880.
HWLKF70	615	830237	1 - 724	15 - 738	AW183080, AI809545, AI693513, AW083841, AI762076, AW362479, AW291420, AW296936, AA657953, AA229394, H91857, AW105152, H91911, AA766735, AF003827, and AA877622.
HWLKL17	616	928720	1 - 422	15 - 436	
HWLKR35	617	918557	1 - 597	15 - 611	AL134524, AL045328, AL038838, AL037436, AL038983, AL047163, AI142134, AL079852, AL047012, AL044125, AL044162, AL040193, AL037295, AL037727, AL038532, AL040621, AL043538, AL043496, AL040464, AL041347, AL037323, AL041324, AL038822, AL041098, AL037435, AL040075, AL040463, AL041238, AL038761, AL037343, AL041163, AL044186, AL047170, AL040617, AL040149, AL043923, AL043814, AL037335, AL047219, AL044037, AL043845, AL040625, AL041635, AL041296, AL045684, AL040294, AL040576, AL041752, AL044064, AL040510, AL041459, AL047183, AL043467, AL041577, AL045753, AL042898, AL041086, AL041246, AL041096, AL043677, AL040839, AL043492, AL041602, AL040444, AL040052, AL046850, AL037443, AL040768, AL044074, AL041730, AL041523, AL043627, AL046994, AL041374, AL040472, AL041133, AL046914, AL043848, AL043570, AL046442, AL042135, AL040322, AL041233, AL041358, AL040119, AL039360, AL045671, AL039316, AL046392, AL041955, AL044272, AL041159, AL041168, AL047057, AL045817, AL044258, AL041346, AL045920, AL134110, AL040148, AL038745, AL041292, AL049018, AL040458, AL044187,

AL041142, AL040332, AL045990, AL041197, AL044199, AL040529, AL040571, AL039643, AL046330, AL041277, AL079878, AL039338, AL040745, AL040370, AL040128, AL047036, AL044274, AL040553, AL040342, AL041186, AL040155, AL040414, AL040285, AL039744, AL040091, AL039432, AL044165, AL042096, AL041131, AL037341, AL043941, AL040090, AL045989, AL041051, AL040168, AL044201, AL046327, AI547295, AL043775, AL043444, AL045327, AL040253, AL041227, AL045857, AL040082, AL040329, AL037279, AL047037, AL041278, AL040238, AL040263, AL041140, AL044529, AL040255, AL045725, AL039915, AL043612, AI526176, AL041344, AL038651, AI547039, D29033, AL049069, AA585439, AL048677, T11028, AL041210, R29445, AL038878, AA585101, AL045211, Z28355, T23957, T23985, C16300, AL043537, AI318479, Z30131, AI547291, D61254, AI525556, AI541383, D57491, AI557084, AI526073, AI547250, AI546875, AI541374, AI541523, AI525431, AI546999, AA174170, AI541205, R29218, AI540967, AL079977, AI546945, AI541508, C16305, D55233, C14723, AI541365, AA585098, AI557731, AA585453, AI557262, AI541514, AI546971, U46344, T41289, D60844, AI546891, AA585476, AI525500, AI526194, AA283326, R28735, AI546828, AI557864, R28895, AI541346, R29177, AL038024, R28965, AI541017, AI547006, AI525306, AB033107, AR064707, AJ238010, AR066494, U94592, I05558, A93923, D50010, D17247, E13740, AJ244003, AJ244004, AJ244005, E03627, I48927, Y16359, AB025273, I84553, I84554, A60212, A60209, A60210, A60211, A98767, AR031566, A90655, A93963, A93964, AR062872, I63120, AR062871, AR017907, D13316, AR062873, A35536, A35537, AF082186, A25909, I06859, A18050, A23334, A75888, I70384, A02135, A04663, A02136, A04664, A60111, A23633, A02712, AR007512, AR038855, A81878, A77094, A77095, I00682, A95051, A18053, A93916, A20702, D78345, A64973, A43189, A43188, A20700, A11623, E00609, A11624, A98420, A98423, A98432, A98436, A98417, A98427, A11178,

						E01007, I13349, A10361, AR043601, A11245, Z32836, A93931, D13509, A22739, A85203, X81969, A16035, E17098, A1133053, A1122101, AR054723, AR023813, A1133074, A1133049, and A22734.
HWLKV34	618	957615	1 - 646	15 - 660		
HWLKV91	619	830214	1 - 513	15 - 527		N54321.
HWLKW0 4	620	969141	1 - 597	15 - 611		AA046825, AA156232, W24222, AA046808, A1074059, AA045655, AA156054, A1079406, A1335087, A1831194, AA927505, A1038824, W20117, A1141175, AA147488, A1085738, A1081430, A1141435, A1086672, A1308846, A1088093, AW263203, A1391491, AA996038, A1146608, A1086624, A1085956, A1095699, A1147805, A1312528, AA888166, AA888822, A1075648, A1041513, A1074781, A1571404, AA927030, AA788786, A1309731, AA863122, A1025254, AA844067, A1073644, A1000826, A1079595, AA960909, W46844, AA576992, AA225982, AA676445, N23131, AA037037, N95533, AA974466, A1741287, W47172, AA975580, A1023076, A1028417, AA862562, N20551, A1203524, F20461, AA854218, A1719742, A1031831, N29263, A1303024, AA137068, AA225981, A1880811, AA071499, AA137139, AA557947, AA470526, N49765, A1017241, AA071339, A1913857, AA082294, H40198, W46671, W61183, AA552473, A1085091, A1192144, H89983, W61182, AA485185, W68371, R78487, AA654079, AA157472, AA302416, AA082321, H81768, A1261461, N90436, AA746698, W37801, AA657730, D11865, A1371356, A1335366, A1345778, AA506060, AW305338, A1345129, AW268293, A1345740, AW303172, A1349836, A1349012, A1289672, AW086304, A1318134, A1310633, A1344902, A1345676, AW302638, A1310894, AW074966, AW301359, A1318161, A1318149, A1335466, A1343156, A1254293, A1345323, AW274108, A1583762, A1613395, A1345208, A1318603, A1318602, AW274347, A1613385, A1224645, A1310790, AW302802, A1252728, A1583885, A1591254, A1336702, A1345422, A1307887, A1817421, A1306231, A1337623, A1343069, A1249590, A1609969,

AI307869, AA366542, AI583839, AA665258, AI612159, AI053766, AI054241, AA651668, AW303152, AI054196, AI802815, AI247156, AI591287, AI249281, AI583652, AI318122, AI001112, AI344894, AI075640, AA844088, AI422646, AA382891, AA046974, AA046881, H98947, AI250125, AA292441, AA292490, AI222305, AI149884, AI341038, AA788814, AA767254, N28749, AI246984, AW272045, AI271500, F29921, AA724648, AI251040, AI053402, AA937982, AF070668, X59375, AL137550, Y10080, AL049382, Z82022, E02221, AL133067, AL122111, Z72491, AF132676, AF061836, I92592, AL133075, AL137480, AF113677, AL137271, AF113694, AF111851, X62580, AF030513, AF104032, AL137557, L31396, X65873, L31397, AF100931, AL122050, A77033, A77035, I48978, AF090896, AL110196, I33392, AL133072, AL133640, AF183393, U68233, A08916, AR038969, AF067728, I89947, A08913, X81464, I42402, AB007812, AL137488, A08910, I89931, A08909, I09499, U42766, AF061573, I49625, AL137459, AF159615, AJ238278, AL117435, U35846, X72889, AR038854, AL122049, I03321, AF113699, A03736, AB016226, E04233, AL050149, AF067790, AF162270, AF111849, AL122098, AF158248, AL110222, U96683, X93495, AL137533, AL110225, AL080124, AL080158, AL137705, AL117460, U68387, AF146568, AL133113, U91329, X98834, X53587, AF118094, A65341, AF118070, AL049314, AF079763, AF000301, AF090900, AJ012755, A08912, AL050366, AR020905, Y11254, A18777, AL137560, L30117, A08908, AF026124, AL137712, AF177401, E12747, AF113690, AL137478, AL133016, AF090901, AL049464, AL133557, AL080137, AL137476, S61953, I48979, X84990, AF113691, AL133014, AL133606, AL137463, AL133104, AL049300, AL080159, E02349, AL117583, AL137538, AL110221, S68736, AL050092, AL050138, A58524, AL133560, AL110280, A93016, AL137429, X82434, AL049938, AL050172, AL050146, AL117649, AL117394, AF139986, AL122121, AF119337, AF113019, AF090934, AL137283, A58523, AF126247, U58996,

						AF017152, AL050116, A12297, AF026816, Y10655, AC002467, AL137526, AF090943, AF118064, E05822, M30514, AF153205, A93350, AL096744, AL117440, AF061981, AL122093, AF091084, I26207, AL133080, AL133098, X87582, AL080127, E08631, AL133077, AL133568, AL137300, AL050393, AL133010, AL117432, AL050277, AF111112, I41145, A18788, AL080086, AF003737, AF113689, AL049466, AL133093, AL049283, AJ000937, AL133081, AL133665, X92070, AL137529, U00763, AF125949, AF113676, S78214, U80742, I00734, X63574, U72620, E07361, AL122110, AF100781, AF017437, I09360, AL049452, AR000496, U39656, AL117585, AL117457, Y14314, E00617, E00717, E00778, Y07905, AL080074, AF081195, AL122123, U49908, AL080060, AF210052, AF097996, AL133558, AF051325, A90832, Z37987, AL137294, AJ006417, AB019565, A21103, AF078844, S75997, E06743, AI250217, and AI334740.
HWLKW0 9	621	951716	1 - 571	15 - 585		AP000500.
HWLKW1 7	622	860227	1 - 218	15 - 232		AA503041, AW013974, AW021078, AI817999, AA856857, AI188696, AI499321, AI815007, AI375786, AI457260, AI472695, AI523679, AA916048, AA909513, AW169263, D53008, AI818022, AA629711, AI041426, AI334313, AI800128, T34424, Z17371, AW090077, AW088569, AI500715, AI149944, AW117620, T68169, AI872743, AI761089, AI671757, H12634, R79928, D57350, AI469660, N73071, T07670, AA648091, T63380, AA666212, AI819847, D57802, and D56837.
HWLLB11	623	954849	1 - 731	15 - 745		AI745636, and AA102414.
HWLLH02	624	918427	1 - 322	15 - 336		
HWLLH25	625	933479	1 - 122	15 - 136		
HWLLS11	626	965899	1 - 731	15 - 745		AA521136, AI002240, AL134536, AW392670, AL119355, AL119341, AL119457, U46346, AW372827, AW363220, AW384394, AL119443, AL134920, AL119319, AL119497, AL119335, AL134902, U46351, AL119324, U46350, Z99396, U46347, U46349, AL042433, AL119484, AL119363, AL119391, AL119444, U46341, AL119483, AL037205, U46345, AI142131,

					AL119439, AL119399, AL119401, AL119522, AL119396, AL119496, AL042984, AL134529, AL119418, AL042450, AL042614, AL134525, AL134538, AL042975, AL042965, AL042551, AL042544, AL043019, AL042970, AL042542, AL043029, AL043003, AL119464, AR054110, AR066494, AR1671, AR060234, AB026436, and AR069079.
HWLLT02	627	918419	1 - 521	15 - 535	AL031652.
HWLLV41	628	830150	1 - 405	15 - 419	AI589207, AC002472, and AC002470.
HWLLX12	629	969681	1 - 399	15 - 413	AC002379.
HWLMA84	630	929421	1 - 202	15 - 216	AA418995, AL121270, AI370623, AL040844, AI862139, AI927233, AW189802, AI522256, AI590043, AI539260, AI540354, AI909661, AL042722, AI307513, AA715307, AA809974, AI633317, AL039716, AI270183, AI582932, AA748353, AI797578, AI434255, AI064830, AI698462, AA761557, AL119863, AI445611, AI758560, AI568293, AI932620, AI683555, AI799313, AI690969, AI417790, AI688241, AI571442, AI282669, AI537273, AI364167, AI468970, AI624543, AI435253, AI638644, AI095003, AA731184, AI909672, AW085181, AI610714, AI919600, H44725, AI698391, AI673395, AI635082, AI439452, AI050084, AI673363, AA814343, AI800341, AA676361, AI866484, AI079226, AI470717, AI679266, AW044367, AI500714, AI610411, AL046466, AI872423, AI524179, AW087540, AW087445, AI918809, AI866469, AI799183, AW081176, AI299035, AI273179, AW128834, AI521560, AW188525, AI915291, AW152182, AI536601, AW262552, AW051088, AF067844, Z13966, I89947, M85164, AR050959, E12888, A65340, AF090903, D83032, D44497, AL110223, AJ003198, AR038854, AF087943, AF000167, U37359, AL122049, AL110158, AL137716, A23327, Y14314, AF129131, AL133051, AI2558, A38574, AL117587, AF141289, AF124728, and AL117416.
HWLN76	631	887583	1 - 522	15 - 536	AA064845, AF126484, AF113925, AF149774, and AC006027.
HWLPC29	632	965058	1 - 603	15 - 617	AA525279, U51700, AI904835, and AL049713.
HWLPG05	633	930991	1 - 330	15 - 344	D60875, D60267, and D60874.



HWLRA85	634	965400	1 - 594	15 - 608	AI493856, AA779066, AI343583, AI668803, AI346964, AI768858, AI984669, AW271303, AI962453, AW044292, AI800575, AI191409, AI692246, AA633357, AA811380, AI142462, AA761737, AA609336, AA568833, AI935515, AW299302, AA599678, AI698071, AI703351, AI445511, AA502281, AA765235, AA663918, AI356972, H00731, AI040729, AW044281, AI817239, AI040041, AI148133, AA760754, AA806273, AI084370, AI088469, AA209476, AA043699, AI167227, AA043649, AI184658, AA255603, AA576467, AA614019, AA285129, AA255580, AA781637, AI984665, AA025353, AA781325, AI949269, AI375319, AI630213, D20127, AA044787, AI918926, AA548537, D58189, AA039984, R59874, AA085467, AI537816, H88293, AW271326, AI862141, AI500111, AI193531, W32202, AA772611, AA187326, AI391515, AA354181, AI355757, AA828122, AA854495, R76720, AA740937, AA49425, H49479, AA417831, R79273, Z40227, AA040631, AA450390, AI754002, W32257, AF053318, and AL122045.
HWLJB86	635	966462	1 - 155	15 - 169	AC008116.
HWLVF04	636	926880	1 - 704	15 - 718	
HWLV006	637	933592	1 - 414	15 - 428	AI628277, AI700170, AI434481, and AC004460.
HWLYS52	638	925738	1 - 493	15 - 507	
HWLXE16	639	975258	1 - 455	15 - 469	
HWLX001	640	913808	1 - 501	15 - 515	
HWLZB12	641	969262	1 - 548	15 - 562	AA917956, AI078015, AA625053, AI308830, AI348305, AI301350, AI343797, AW339860, AA837028, AI275863, AI025643, AI025649, and AJ236591.
HWMAD05	642	931076	1 - 396	15 - 410	N86362, AA565006, F26713, AI434037, AA347382, AI064843, AA078184, AA745543, AI368732, AI133612, AA165505, AA515742, AW419389, AA630122, F24745, F23287, AA165346, AI686470, AI433104, AW243884, AA568314, AA595661, N44129, AA229422, AA214042, AI811647, AW105729, AA847102, AA460896, AA728880, AA303011, AC007462, AI132777, AC008009, AC006441, AF001550, AF217403, AI035072, AI022718, AC004884, AC006443, AC006323,

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HWMEI07	643	830227	1 - 302	15 - 316	AW148716, AI917055, N42321, AL038605, AI802542, AW302965, AI815855, AI340603, AA427700, AI308032,

AI569583, AI312428, AA225339, AI269862, AI962858, AI571909, AL048656, AI521012, AL079963, AA640779, AW103371, AW403717, AL045266, AL039086, AI497733, AW023590, AI890833, AI926790, AI687127, AI590120, AI064830, AA572758, AA508692, AI564719, AI889376, AW268220, AL119863, AI349645, AI619502, AI677796, AL121365, AW026882, AI815232, AI344785, AI783504, AI536638, AI524671, AI554245, AL042382, AL045500, AI433157, AI343059, AI702073, AI340627, AI349933, AI468872, AA287231, AW238730, AL119457, AI921248, AL047042, AI886753, AW087445, AW150578, AI620284, AL036403, AW132056, AL044207, AL036274, AI282326, AI922901, AL036396, AI340582, AL036146, AI349937, AI537677, AW071417, AW301409, AI308035, AI500523, AI281773, AW168795, AI500706, AL040243, AL121014, AI284131, AW068845, AW102785, AW103893, AI561299, AI269696, AL037454, AI648663, AI800453, AI800433, AI868831, AI888953, AW020693, AL120853, AI334884, AI633419, AI348897, AI498579, AI445165, AI866002, AI433976, AI828731, AI251830, AI036802, AW169653, AI648684, AI687065, AI612759, AL041772, AI610645, AI869367, AW148320, AI784252, AI340519, AI608936, AW075413, AI500077, AI919345, AW088903, AI036361, AI439717, AL041150, AI274508, AI366549, AI636719, AI539153, AI309401, AW022682, AW268067, AI539771, AL038779, AI567351, AW074993, AI431424, AI349614, AI866608, AI343112, AL038565, AL036980, AA613907, AI539808, AI862144, AW268253, AI567612, AW301300, AI349598, AL036664, AI349256, AW075207, AI433384, AI312152, AL079741, AI345735, AW274192, AI345551, AA974049, AA493647, AW075084, AI281772, AI950664, F27438, AW193134, AW105601, AW074869, AW089572, AI307543, AI307210, AI307708, AI500659, AI312325, AW088134, AI753683, AW079368, AI313320, AI612885, AA804740, AI307520, AI284517, AI923989, AW302992,					
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HWME148	644	830256	1 - 252	15 - 266	AC004777.
HWME65	645	969190	1 - 582	15 - 596	AC006237.
HWMEU56	646	922375	1 - 487	15 - 501	
HWMF28	647	965354	1 - 437	15 - 451	
HWMF10	648	963406	1 - 578	15 - 592	
HWMF32	649	883180	1 - 360	15 - 374	AA491767, H58891, AA515723, N69399, T40210, H73306, AA366601, AI590592, AI479148, AA486573, AW302923, AA846482, F34605, AI133083, AW089016, AI355873, AI620415, AL122020, AC004876, AC005585, AC005089, AL031311, Z93023, AL035697, AC007363, AC006020, AC002456, AL049830, AP000355, AC002312, AC004491, AC000379, AC007543, Z98742, AC005215, AC007637, AC007546, AF017104, AC002565, Z82205, AL034421, U80017,

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HWMFH23	650	849129	1 - 332	15 - 346	
HWMFQ90	651	928646	1 - 347	15 - 361	
HWMFY21	652	974325	1 - 570	15 - 584	
HWML13	653	947969	1 - 411	15 - 425	U37501.
HWMHG0	654	933534	1 - 615	15 - 629	
HWMHG2	655	957665	1 - 512	15 - 526	AA707467, AW292400, and AL122104.
6					

HWMHS10	656	961647	1 - 742	15 - 756	
HWMHT22	657	917570	1 - 667	15 - 681	AL117342.
HWMHX1	658	914007	1 - 724	15 - 738	AF048727.
2					
HWMHZ25	659	951699	1 - 341	15 - 355	
HWMID39	660	915686	1 - 490	15 - 504	
HWMIR03	661	922302	1 - 322	15 - 336	
HWMJB68	662	914031	1 - 386	15 - 400	AI431513, H53217, H60249, R95840, N72170, AA470567, H66577, AW167773, AL048275, AA975894, N22465, T50061, H78898, AA503298, AI371208, AA299589, AI565126, AI610737, AA405726, AA492105, AW068580, AA303131, F00564, AW089916, AA713705, AA368155, AI678992, F35663, AW021674, AI745335, AA015948, AC002302, AC005520, AL031228, AC005409, AP000692, Z86090, AC006449, AC004253, AL035071, AL033521, AC004526, AC004967, AC002425, AL109952, AC004796, AL035405, Z85987, AC005620, U91326, AC002544, Z83308, AC003101, AC007687, AC010582, AC004148, AF049895, AC006316, AC005284, AC004890, AC007226, AF196972, AC005484, AC004000, AC007216, AL133448, Z83844, AC006511, AL049760, AC007637, AC003695, AC000025, AL096701, AC000385, AC005527, AF053356, AC004757, U63721, AF196779, AL022322, Z97876, AP000252, AL049839, AC005962, AL109984, AC002115, AL035420, AP000212, AP000134, AC007376, AF038458, AC004150, AC005846, U95742, AC005015, AL021397, U47924, AF134726, AC007387, AC006071, AC004491, AC005971, AL049776, AC004686, Z83826, AC007308, Z83843, AC005529, AL096791, AF165926, AC002470, AC005200, AC005519, AC006211, AC006057, AC004805, AC005488, AC007225, AC005697, AC006581, AL008582, AF045555, AC005777, AC005081, AF047825, AC005383, AC002045, AC005399, AC005031, Z98036, AC004975, AL080243, AL035587, AC009464, AC002476, AC004644, AL121603, AC006512, U80017, AP000512, AC005829, AC005370, AC006088, AC004832, AL022476,

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HWMJE50	663	933501	1 - 104	15 - 118	
HWMK101	664	913841	1 - 658	15 - 672	H43471, AI859744, AA635433, AI299882, AA071151, AW272815, AI679871, AI251024, AI309979, AA282951, AI479148, AI929796, AA610255, AI962030, AA743996, AA984829, AI932871, AL037714, AA602017, M78032, AA515728, AI636734, AI623364, AA397821, AL134216, AA722505, H43183, F18761, AA368155, M78026, AW341955, AA115865, AA557945, AA488687, H87936, AA469327, N68677, AI678476, AA643770, AI282629, AA846923, AL037856, AL042373, T07225, AA533408, AW408596, AW238495, AI348780, H77492, AI358514, AC004491, AL109865, U91327, AC004967, AC004000, AL022322, AC006509, AC005777, AL031282, AC007666, AC005516, AC000052, AL035089, AL031666, AF134726, AC006001, AL023879, Z95116, AC005082, AC005736, AL034420, AB023050, AC007030, AP000347, AL049872, AC000353, AC004033, AC005067, AC005602, AL035405, AL049776, AF196779, AL022318, AC004796, AP000346, Z98036, AC005500, AL035086, AP000694, AC004883, AC005274, AL049780, AP000313, AC002316, AC002425, AC015853, AP000547, AL031291, AF111167, AP000050, AL031681, AC005578, AB001523,



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HWMKI10	665	961616	1 - 513	15 - 527		AA365382, AF155219, AF149877, and AF126427.
HWMLG23	666	961110	1 - 233	15 - 247		AA353040, AA383720, AA382189, AA133917, AI751877, AA315963, AA057016, R13065, AF151802, and AF042284.
HWMMA1 2	667	969173	1 - 240	15 - 254		AW138984.
HWMMG6 5	668	928823	1 - 768	15 - 782		AW139091, AI434608, AA653723, AI658553, AI418050, and AI675691.
HWMMS6 5	669	917513	1 - 603	15 - 617		
HWMMY6 6	670	966367	1 - 394	15 - 408		N22506, AA358178, AL117339, AF205588, AL022345, AC005815, AC004126, and AC007766.
HWMNC07	671	951724	1 - 37	15 - 51		
HWNAG05	672	928811	1 - 711	15 - 725		AW170560, AA635931, C17038, C19030, R11094, and D78833.
HWNBJ06	673	933578	1 - 302	15 - 316		AA213877, AL119483, AL134538, AL134920, U46349, AL043029, AL119355, AL134531, AL134533, AL043011, AL119497, AB002334, AR060234, and AB026436.
HWNBS06	674	933587	1 - 399	15 - 413		T28503, AW301137, AL079683, Z98473, AA832148, AI344844, AA483211, AA584749, H16048, AA192695, T12272, T11542, AI951495, AI688846, AI345654, AI471691, F19258, AA457639, AW081359, AI015912, AA443065, AA366986, AA368745, AW276827, AW193432, AI205126, AW439558, AA515051, AI633478, AA843450, AL119391, AI282907, AI270343, AI352078, AI345522, AA079528, AI557323, AA338431, AI340453, AI184226, AA665192, AI890928, AI890570, AA659083, AW265197, AI284640, AI914706, AL133723, AI358343, F31204, AI889781, AA745560, AA745431, AA569284, AI801600, AW269639, AW238016, AW023672, AA515128, AI064952, AI633390, AI246796, AA658235, AI879000, AI433187, AA176924, AI674873, AI053786, AI721122, AI768968, AA169801, AA558003, AA779018, AI951436, AL041412, AA252620, AL042753, AI354540, AA364567, AA229785, AA457482, F28576, AI567786,

AA775230, AA973575, AI569086, AA515435, AI138344, AA551509, AI349874, AA828856, AI038279, AW337985, AA682189, AI079910, AW243706, AA435854, AA837755, AA745362, AI252085, AW130799, AI445436, AI890052, AI252114, AI963786, AI890923, AI792903, AI274431, F31796, AI792864, AI733957, AI734002, AI929531, AI079645, AI431303, AI003743, AI003172, AI561335, AI679713, AA362700, AW162049, F31799, AL042856, F37223, AL046409, AI709365, AA501614, H64560, AA878954, AL040324, AW264973, F37286, W60516, AI493634, N99715, AW074398, AW172727, AW090811, AW193265, AW265393, H94871, AI474713, AA736963, AI872421, AI050007, F07193, AA630352, AW080134, AI678392, AA654979, AL120235, AI049722, AI345157, F24284, AA353408, N71724, AA652329, AA492244, AI124660, AI149915, AI345161, AA348402, AW104748, R97987, AI962050, R99852, AI350211, AI608626, AW238278, N74620, AA354311, AI341664, AW020483, C06327, AA579249, AI061334, F36273, AI435544, AA524832, AI039451, AA482711, AI287964, AI917271, AW169230, AI499094, AI471709, AA515224, AI471481, AW166815, AI939465, AI521618, AW069807, AA743956, AI613280, N25042, AI133721, AL046782, AI963720, AI761471, AI366071, AI679782, AI904894, AA470581, H13868, AW274064, AI914151, AA308806, AW327360, AA781504, AL038785, AW103415, AW270284, AW419118, F29989, AI818332, N43757, T40617, AA626678, AA535661, AI225141, AW406755, AI708009, AC005339, AC002492, U86136, AI035587, Z99916, Z83845, AC004152, AL132800, AI034429, AC003957, AC007878, AL022315, AL022166, AL031665, AB020862, AC004864, AL031673, Z98747, Z98950, AC007637, Z84484, Z82206, AL031279, AC006013, Z82188, AC005094, AC018633, AF001552, I35668, AF135187, AC005612, AI050348, AL035703, Z95114, AL021395, AC008062, AI133297, AL035685, AL035588, Z85987, LI3709, X03273, AL031296, Z72519, AC007388, AL022238, AC005386, AF001905,				
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HWNCY59	675	927487	I - 224	15 - 238	AA458703, AA476397, AA937427, AA618452, AI334443, AA508359, AW270343, AW440497, AA126519, AL038705, AL045053, AA082567, AI792231, AA551552, AA482953, H53828, AI754253, AW084466, AW193410, AA216412, AA508902, AA547947, AL119691, AA657835, AW081165, AW275510, R73380, AA468244, W93917, AI002744, AA490183, AA431949, R02632, AI004704, AW192179, AA478355, R44116, AW238121, AA493975, AI306191, AI305894, AI754653, AA838190, AI110844, AW302087, AI766906, AI954260, R45369, T69264, AW302080, AC004675, AC004656, AF088219, AC002123, AF165926, AC007510, AC005233, AC007564, AJ011930, AC005832, AF031078, AF030876, AL121652, AC005015, Z98884, AB026898, AL078638, AC007546, AC006965, AL031681, AC004815, AP000213, AP000135, AP000031, AC005399, AC005224, AL031311, AL035685, U95742, AL035423, AC007688, AL023799, AC007172, U91323, AC004841, AC007536, AC005291, AC016026, AC008014, AL020996, AC006978, AC004881, AC007566, AL031428, AC004159, AC002553, AC007537, AC002449, AI096711, AC003101, AL034402, AC006501, AC003029, AL031283, AC006333, Z98941, AL109984, AP000347, AC002289, AP000100, AC007226, AC005409, AC007161, AC005529, AC005229, AC004813, AC004230, Z83838, Z95116, U29953, AL035587, AC002991, AL035450, AC004821, AL049830, AC005280, AL049699, AC005480, AP000704, AC004549, AL031594, AL021393, AP000553, AC008044, AC007052, AL008732, AC005207, AP000498, AC004167, AC005069, AC009411, AC002470, AC005414, AP000556, AL035603, AF207550, AP000552, AC005971, AC005920, AP000008, AC005620, AC004019, AC005011, AP000959, AC008170, AC008372, Z93023, AC005932, AP000967, AC004934, Z81369,

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HWNE076	676	929720	1 - 347	15 - 361	AC005752.
HWNE05	677	928784	1 - 231	15 - 245	
HWNE06	678	933551	1 - 1000	15 - 1014	AA193123, AI911922, AI379417, AI076484, H98484, D62790, and AC004219.
HWNEZ48	679	933522	1 - 388	15 - 402	AC007227.
HWNGN09	680	961602	1 - 442	15 - 456	AL045232.
HWNHAI2	681	969205	1 - 769	15 - 783	
HXOAI14	682	974075	1 - 622	15 - 636	R82572, AI046024, AI048523, I05966, S50263, M31555, E06646, M16072, A29575, I25725, X72796, A73099, AF045504, AB016619, AF031634, Z15023, AF045485, Z21680, AF045486, M19900, X65087, L14358, M17770, S82492, M60239, AB028875, Z15019, AR034680, DI2736, S67223, AJ242621,

					M31278, Y13990, AF045505, M58570, A47281, D12730, AJ002433, U56408, U85491, U17476, A82600, A82599, Z15021, Z15022, M60249, L14356, M30483, L14357, I07390, Z15020, M90468, M36208, X74589, M34525, A43173, M30482, L14369, U88067, M27584, AB006832, Y17374, AF113109, L14368, U80190, M60745, AF056216, M83537, D14175, U50329, AR007979, M36230, S63552, D25498, AB015881, M27583, X65089, L14362, L14363, M90690, AR014066, L14366, D14174, M36233, X70098, M36214, M97872, M95938, X67796, X65088, X67800, X03301, A22466, X59174, A22469, X70096, AR007981, X70091, L30138, A57333, AR003778, A22539, A22470, A50960, A57349, A57353, A50995, L31895, A50993, A57337, A57341, A57351, A57343, A57345, A57347, L14365, X65090, AF127458, U89324, A38268, A38267, M91699, AJ250900, AF045023, X59210, L14367, AJ005354, L14364, M24786, X03300, AR059286, AF023242, U39900, U39899, M54977, M24785, X67190, X67191, M28834, A13735, A23165, L02346, U00927, M97861, X00894, AF045892, M19903, X57857, S72514, A44967, E08434, AB001737, AF134808, AF045895, U24114, M84437, E16346, M97876, E03802, I31960, M20835, AR042571, L24918, X14623, and AJ131750.
HXOAA67	683	974326	1 - 372	15 - 386	AC007240, AC004104, AP000316, AP000118, AP000165, and AL023883.
HWNHN10	684	961609	1 - 659	15 - 673	AA912130, AI240479, AA815414, AI809506, and AA969138.
HWNDU11	685	965382	1 - 479	15 - 493	AA195743.
HWNCN05	686	928791	1 - 942	15 - 956	N93301, AI039653, AW268575, W25153, AI818415, AW271345, and AI675486.
HWNBX05	687	928800	1 - 402	15 - 416	H11279.
HWNBLL2	688	969222	1 - 432	15 - 446	AL135067, AI378370, AI351880, AI138478, AA679780, and AC006344.
HWNAI06	689	933591	1 - 466	15 - 480	AA453147.
HWNAE01	690	914082	1 - 1052	15 - 1066	AA705184, AI247864, N92043, N68830, H53322, R50487, H53323, AI379225, and R50572.
HWMG01 0	691	961716	1 - 303	15 - 317	AW085802, W15495, AI510780, AW070676, AA678924, AI096738, AI699147, AA722955, AA228292, AP000692, and

HWMBY62	692	937234	1 - 665	15 - 679	AB023150. AA033973, AW204163, AI1818304, AW081429, AI214706, AA399495, AA525779, AA631754, AA398154, AA515710, AA190519, AA190482, AA365169, AF109219, and AL137607.
HWMBM8 9	693	968984	1 - 491	15 - 505	AI762892, AI760766, AI189223, AI824008, N30895, AI927354, AA443809, AI372949, W81043, AI299589, AI934550, AA605197, W81079, AI168782, AW374587, AI538814, AW079505, and AA447177.
HWMAE12	694	969692	1 - 728	15 - 742	AA492421, H51230, AR028772, AC004601, and AC005684.
HWLXJ10	695	963328	1 - 521	15 - 535	AW000952, AW451313, AW028154, AW235849, AL042898, AL134524, AL045328, AL045327, AL047163, AL134110, AL037295, AL038838, AL038983, AL037335, AL037343, AL037323, AL037436, AI142134, AL047037, AL038878, AI547295, AL037443, AL037727, AL038532, AL038822, AL038761, AL037435, AL135012, AL040576, AL041955, AL045753, AL040472, AL039643, U46344, AL038745, AL039360, AL038651, D29033, AL049018, AL045891, AL048677, AL043089, AL042655, AL039432, AL043321, AL038040, AL043941, AL045494, AI318479, AL042523, AL048657, AL046356, AL038041, AL042420, AL042741, AL038024, AL042468, AW363350, AI547258, AL031651, AR066494, AL133053, AL122101, AL133049, DI7247, A93923, A93916, A93931, A85203, AL133074, and AR023813.
HWLVU33	696	972979	1 - 525	15 - 539	AA775419, AI273235, AI754154, AI446402, AI640735, AI468600, AA602645, AA460180, AI675266, AI382693, R40043, and AA813916.
HWLVK02	697	922696	1 - 580	15 - 594	AA916685, AI913975, AI186460, N64366, AW003622, AI209045, AW383922, AI186495, AA988844, and AA505627.
HWLUY15	698	874966	1 - 455	15 - 469	AA813464, and AI299894.
HWLQS70	699	933799	1 - 615	15 - 629	AI692670, AI983514, AI659461, AA857943, AA848022, AW023325, AA150963, AA856775, AI333521, AI350586, AI057121, AI743582, AI093682, AI039079, AA811978, AA621091, AA737208, AI350364, AA522951, AW302375, AI381406, AA639131, AA903924, AA890276, AA210835, AA258236, AI690470, AA214632, AA736622, AI015154,



HWLQA64	700	918932	1 - 237	15 - 251	AA701126, AI015739, AW149922, AA259080, and AA743600. R44785, AW296584, AI698918, AI435319, AI124890, N26029, AI652245, AI524315, AA243863, AI743693, AI148476, AA830427, AA934726, AI828768, AA481312, N27950, AA602331, AA918069, AA463272, AI431707, AI858382, AA644278, AI990803, AI081819, AI264927, AW274632, AA283019, AI379553, AI830530, AA195654, AA234974, N67908, N62389, AW300062, H97988, AA772368, AI824287, AI590043, AL045619, AI866465, AA641818, AI539800, AI815232, AI868204, AI500714, AI355779, AI581033, AI537677, AL046466, AA715307, AA809974, AI538885, AL042416, AI582932, AW025943, AI889189, AI554827, AW055075, AL046618, AA761557, AI801325, AI859991, AW162194, AI872423, AI494201, AI521560, AI500659, AI500523, AI538850, AI471909, AI366900, AI923989, AI284517, AI500706, AI445237, AI491776, AW151138, AW151974, AI500662, AW172723, AI284509, AI440263, AI889168, AI866573, AI633493, AI434256, T99953, AI273179, AI805769, AI434242, AI888661, AI284513, AI888118, AI436429, AI889147, AI371228, AI440252, AI491710, AL047422, AI866786, AI860003, AI610557, AI242736, AI433037, AI887499, AI539781, AI539707, AI433157, AI923509, AI559957, AI521571, AL043168, AL042488, AI671642, AW161202, AI439995, AI089469, AI890907, AI582912, AI364788, AL039390, AW083804, AI539771, AI343091, AW191003, AI309443, AI570774, AI828574, AI923046, AI349276, AL048375, AI269862, AI887785, AA748353, AC005575, S68736, X72889, AI122049, AI133637, AL133113, X80340, AL133072, AL133080, AL122110, AL133081, AL133077, AL137283, Y10655, AL122050, AL049423, X70685, AL117583, AF081195, E07361, I17767, U90884, AL137526, AL133640, I46765, AL117585, AL117578, U49434, and AL122123.
HWLPN12	701	969572	1 - 445	15 - 459	AI004958, AA481489, AA481174, F00376, T17269, AA503168, AA664604, AL037910, AI292236, AL046782, AI633168,

AW338508, AW082744, AI582890, AA342562, AI357823, AA878149, AI952900, H62778, AA653612, AA665645, AA654321, AI049996, R92640, AI826845, AA577732, W45355, AA323085, AA603323, AI538540, AW021917, AA558298, R82388, W44373, AA297538, AA758266, AW117740, AA086318, AA582554, AI748803, AW148792, AI124798, AI678392, AA878140, AI830390, W01998, AA878431, AA037110, W01999, AW068316, R79597, AI536625, AA593471, AW082117, AI119555, F23255, H84359, AA634837, AI569982, AI709096, AA720732, AA477103, AI049598, H82330, AA879053, AI753113, Z85986, AC012599, Z99127, AP000502, Z96050, AI117352, AC002040, AC006318, AI031277, U62631, AC007347, AC002347, AI031120, AC002544, AI035460, AI134726, AC006254, AC007030, AC004765, AI109798, AC003043, AF117829, AC004222, AP000514, AC004448, AC003029, AC007637, AI031283, AC004859, AF003626, AC006262, AC004003, AC005300, AB020868, AC007736, AI022313, AI246003, AI031650, AI008708, AC007666, AC006257, AC006013, AC005592, AI031282, AI031276, AC004256, AC004090, AC004983, Z82201, AC006538, AC004595, AC005529, AC005179, AC002073, AI049745, AC006312, AF037338, AC005288, AI132777, AC006026, AC007055, AC005839, AF121781, AC005377, AC003663, Z95331, AC004841, AC008012, AC005899, AC005921, AC006137, AI021395, AC004990, L29766, AC009514, AI023283, AC004150, AC000026, AC006132, AI021155, AI023879, AP000115, AI034417, AC002115, AF037222, AC002059, AC005531, Z84480, AI035415, AC005102, AI050306, AC006017, AC004655, AC005157, AI121769, U95742, U78027, AC004087, AC005358, L32588, AC004890, AI133448, AC006480, AC007216, AI031659, AI024509, AC007566, AC007671, AC005005, AI049795, AI049591, U82757, AC008498, AI035422, AB015355, AI031289, AI136295, U63721, AC005696, U91326, AC005520, AC005823, Z82244, AC003049, AC005745, U50537, AC006960, AI022068,

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HWLOI02	702	918320	1 - 424	15 - 438	AW205701, AA885386, AA639272, AI185575, AI095130, AI539690, AA765760, AW150557, AW301409, AI866465, AL045995, AW022713, AA668621, AI859899, AI680221, AW129117, AI285448, AW079511, AI521136, AI373276, AL038185, AI913476, AL042899, AI042898, AW020693, AI921155, AC006313, AL049426, AF106657, and AF118070.
HWLOB68	703	908500	1 - 592	15 - 606	N20488, N25521, AW392670, Z99396, U46347, AL036418, AL038837, AL037051, AL036725, AA631969, AW384394, AL039074, AL119484, AW363220, AL036924, AL036858, AW372827, AL119457, AL038509, AL043003, AA648406, AL039564, AL039085, AL119497, AL039156, AL119439,

HWLNC88	704	875790	1 - 558	15 - 572	AL039108, AL119319, AL039109, AL039128, AL119324, AL036190, U46351, AL043147, AL119443, AL037639, AL119391, U46350, AL037094, AL036767, AL039659, AL119522, AL037526, AL036196, AL119483, AL119363, AL119355, U46341, U46349, AL038531, AL119341, AL119396, AL119335, AL134519, AL037082, AL037077, AL119418, AL042909, AL134132, AL038520, AL119496, AL039625, AL039648, AL134530, AL045337, AL134531, AL134527, AL134528, AL119444, AL037205, AL036268, AL134533, AL042975, AL039678, AL039629, AL039386, AL037027, AL037085, AL134538, AL039423, U46346, AL037615, AL038851, AL039150, AL040992, AL042614, AF205588, AJ245586, AJ245587, AR066494, AR060234, A81671, AR023813, AR064707, AR069079, AB026436, and AR054110.
HWLNA36	705	974863	1 - 636	15 - 650	AI634844, AI039734, AI373240, and AA558783.
					AI767588, AI635347, AI640606, AI991689, AA977785, AI979247, AA971157, AI687230, AI873792, AA152394, AI244588, AA761110, AI126673, AA491080, AA679080, AI913234, AI920850, AI018184, AA702114, AA377229, AA436906, R81654, AI741350, R50230, AF222340, AF106037, AF183569, and AB011097.
HWLMI16	706	918726	1 - 387	15 - 401	AA427809, and T10788.
HWLLZ91	707	887157	1 - 451	15 - 465	AL022322.
HWLLD02	708	930932	1 - 418	15 - 432	AI452848, AW296319, AA928929, AI333232, N67650, AA558581, R37383, AI689843, AI002814, Z39760, R66421, AA634494, F09812, R43751, W37287, AL047118, T72545, H39739, F02269, AA214212, H21614, AI298767, AW294091, AW008823, AA127563, and AI421390.
HWLKT19	709	974292	1 - 494	15 - 508	AL119483, AA084401, AA714605, R48980, AA527963, AA149475, AA654482, AI475870, AW162750, AI362694, AA663074, AI928890, AL134920, AA309318, N23095, AW327422, AA020882, AC004167, AC006971, AC006543, AC006544, D86995, AF111168, Z92846, AC006251, AL080317, U66061, AI035658, AL021917, AL117351, AC008115, AC004890, AC006312, AC007387, AC007371, AC005736,

AL049779, AC003103, AP000692, AC004884, AC007199, AP000141, AC004858, AP000088, AP000696, AC004770, X87344, D87675, AC000134, AL031659, AF030453, AC005088, AL031278, AC006530, L44140, AL031774, AC002492, Z82190, AC004031, AC004079, AL031293, AL035458, AC005630, AC002400, AL035405, AC010206, AC008119, AP000555, AB000876, AC004181, AC004841, AB000882, AP000346, AP000501, Z69721, AC006146, AF109907, AF161221, AP000300, AP000045, AP000113, AF020662, AC005233, AL031257, AC005914, Z94277, AP000697, U95626, AC002994, Z82198, AC012085, AL080243, AC004887, AC004805, AC005740, AL008718, AF001550, AC000035, AC003695, AL031577, Z97053, AC002395, X89814, AL049856, AP000295, AC005480, AP000111, AP000043, AP000128, AP000206, AC004929, AC004150, Z84466, AC004477, AP000245, AC007011, AL035086, AL133448, AC007773, AC005529, AC006285, AL079342, AJ251973, AC002375, AC004242, Z98742, AC004883, AL121603, AL009181, and AC005921.					
AA825330, AA100338, AA313691, AA127036, H19273, AA025872, AA081777, AA360187, AI272649, AW388050, F34605, AW071109, H48768, AA358288, H68343, AA516214, H40478, AA643784, AA515728, AI811685, C75139, AI096714, AA772873, F24284, AA745302, AW245354, R96427, AW337805, R98218, AL079894, AW373645, AA602458, N34258, AA664924, AA565911, AI890971, H81406, AA653955, AI799569, AA808847, AI446259, AL048479, AW084431, AA315052, AI049709, AA447006, AA838192, AA323644, AI633386, AI192440, T86603, AA516328, T60316, AA653713, AI821382, AI820534, AL047480, AI921765, AA368659, AA525407, R67086, AI564215, AI003391, T85570, AW023515, W02749, AA349746, AA654482, AW408756, AA361513, AA365056, AA714899, AA808843, AA618316, T05617, AI207476, AA632993, AW162750, AW022891, AW074210, AA297698, AI299192, AW245860, AL134527, AA828834, R48980, AA577727, D87453, AF196971, AC006962, AC004757,	710	965390	1 - 163	15 - 177	
HWLQ11					



					AL031588, AC004583, AC009396, U91324, AC004491, AL031387, AC007773, AC004025, AL135960, AJ131016, AF111167, AC007308, AC002470, AC004771, AC005756, AC004707, AC005808, AF111169, L12582, AC005722, M64093, M29929, Z95115, Z49154, AC004030, AC005952, Z83733, AC004131, Z98743, and AL049749.
HWLJKJ18	711	930414	1 - 798	15 - 812	AI270326, AA747375, AI446205, AW407919, AI927094, AW189068, AI683294, H54340, AA324186, AA593471, AI160117, AA469327, AA744272, R70333, AA744001, AA779783, AA745524, AI303008, AW270768, AA551798, AA744455, H21488, AA342256, AI245423, F04697, AA745588, AI672135, AA371567, F37169, AA085587, AA743966, AA603264, AI367523, AA586433, AA502568, AA716755, AA635433, AI264743, AA664604, AA846923, AA484228, AA342189, AW265393, AI284108, AI081147, AW008074, H58472, AI590404, AI568683, AW088130, AA669522, AA599080, AW104163, T40848, AA206629, AI148245, H91706, AW238016, AA828860, AI291037, AL043721, AW078909, AA284062, AA604395, AA350596, AA937686, AI701959, AA654482, AA228824, AI932871, AA358086, AI360514, AI583142, AI418529, AW277174, AA604843, AI798041, AI689019, AA557486, AW102955, AI917982, AW265009, AW440549, AW440492, T47739, AI978712, AA781504, AI367721, AA657741, W23546, AA384039, AA262752, AW406659, AI870453, AW069450, F03525, AI168205, AW085626, AW088559, AA568947, N45056, AI352078, AI570943, AL049872, AP000344, AL009181, AC006354, AC005667, Z82900, AC004929, AB011134, AC006014, AC008064, AL035400, AP000345, AL110122, U73638, AC005914, AC004211, AC006121, AI135745, AL023799, Z86090, AC005531, AC005206, AC005327, AC006441, AC006952, AC005264, AC006017, M87914, AC002425, AP000502, AC002422, AB023049, AC005911, AL121655, AL049829, AP000512, L78810, AC004973, AC003035, AC006312, AP000694, AC002126, AB023050, AL080243,

AP000133, AP000211, AC004820, AC003078, AL078463, AC004815, U07562, AF019413, AC003973, AC005105, AL020997, AC005480, AC005828, AC009509, AL022726, AL034430, AC004470, AC008041, AC004963, AC006538, AC006953, U07563, AC003684, AP000511, AC004837, AC005768, AC005180, AL078639, AC002347, AC003664, AC004797, AL031257, AC003101, AL050318, M90058, AC006511, AL031774, D00591, U69730, AC005988, AC007686, AC006388, AC004383, AC005049, AC004595, U73636, AC011421, AC005785, AC004854, AC003104, AC005071, Z98051, AL031848, AC002055, AL049611, AC005280, AC006048, AC005619, D26067, AC005146, AC005971, AL117337, AC006468, AP000500, AC006111, AC005902, AC006327, AL096701, AL034370, AL096827, AP000557, AL035427, AC005877, AC005089, AC006021, AC004996, AC007731, AC005500, AL135744, AC004151, AL079334, AC000094, AC005903, AF112482, AC000085, AC003957, AC005245, U02068, D88268, AF205588, AP000509, AL133163, AL132987, AC007842, AC005081, U91321, Z81313, AC002045, U63630, AL021155, AL031053, AC005370, AC002301, AC006581, AC004975, AC004745, AL096791, AC004972, Z99716, AC004805, AL031393, AC007066, AC005192, Z98941, AL022315, AC004881, AL078621, U82828, AC006208, Z82214, AF064864, AF165176, AL035450, AC010168, AC006449, D84394, AC002511, AC001234, AL117328, AC006285, AC005232, AC005193, AL031577, U73332, AC005913, AB017602, Z30993, Z84721, AL035252, AC005316, AL034402, AC004976, AP000356, AC005317, AL035410, AC005399, AC006079, AC006162, AC008079, AL031676, Z95331, AC003070, AC004596, Z98052, AL024498, AP000116, AC004817, AL008637, AC005102, Z99943, AL022476, AL136295, AC007542, AJ251973, AC005011, AL079295, AL121653, AL049697, AL008718, AC004531, AC006965, AC004955, AL121658, AC005007, AC006427, AC004782, AC006211, AL109827, AC006042, AC006084, AC006088,



						AC007064, AC005839, AC005778, AL022396, AC004032, Z49235, and AC008040.
HWLJK03	712	922371	1 - 520	15 - 534		AA902430, AI681252, AI879991, AI080276, and AF202257.
HWLJW12	713	969556	1 - 560	15 - 574		AW054698, AA642512, AI378060, AA494486, AA536108, AI823838, AA502907, W56244, AI963205, AA663127, AA587968, AI859142, AW069188, N23036, AI024942, and AI117639.
HWLJW11	714	924518	1 - 500	15 - 514		W60263, AA781074, AA004225, AI698018, W04286, AA235149, AI948978, AA977744, AW013825, AW301584, AI719432, W60314, AW392370, AI678934, AA747067, AA746945, AA234751, AW382644, AA654607, AI349272, AA307294, AA307292, and AC004985.
HWLJU91	715	789882	1 - 501	15 - 515		AI660842, AA132964, T70354, AA587170, AI473318, AW339181, and AI471705.
HWLJP28	716	925655	1 - 440	15 - 454		N95385, AW083800, AA996318, AI271604, AI084115, AA854349, AW276544, AW247346, AI373017, AW001509, AA195247, AI139246, AI139463, AI066681, AI066683, AI884736, AI948653, AA463989, AA243640, AI188854, AW001474, AA973976, AA514447, AI523850, AI082808, AI223410, AI288210, AW246721, AI870011, AA861211, AI471823, AI693037, AA421035, AI086153, AI768262, AW005672, AI159904, AA515681, AI621122, AI379956, AW196296, AI697046, AW054883, AI208302, AI359604, AA176600, AI634195, AW341997, AI298008, AA148653, H23135, AA481989, AW069378, AA176960, AA399227, AI351955, AI202782, AA906678, AA258378, W74136, AI589127, AA745713, AA706773, H39661, AA828210, AA481999, W79674, AI183872, AI272018, AA768685, AA176831, AA977112, T33485, AA989448, Z41804, AI359380, AA368962, AA865669, AA975159, H89978, AI432354, AI911220, AI015167, AI418891, AI383671, F26818, F17274, AI972992, AA748828, AA458602, AI865762, F03711, AA599652, D19842, AW388587, AA291674, AA292183, AA975485, F29808, AA481856, AA481836, AA421034, AI219176, AA405298, AI362948, AI133634, AF159063, and

HWLJM40	717	710519	1 - 546	15 - 560	AF112215, W60827, and AL047234.
HWLJK01	718	914089	1 - 616	15 - 630	AA746173.
HWLJS95	719	795416	1 - 255	15 - 269	AI699874, H51304, AI783850, R18531, AI690301, H51898, H02058, AA761876, AA769559, AA601182, AA485941, AA634147, AA374166, R60198, T47172, AI124664, AA314294, R79025, AA468322, AI027602, AI925653, AA305334, AA487500, AW195949, AI922828, AA708021, AA069589, AA059369, F00487, AA632845, AA745581, AI924702, AL040573, AA032022, AA031911, AA312605, AA429675, AI014920, AA324750, AA664564, AA555313, AA907537, Z99496, AC005279, AC005567, AL050312, AC002312, AC005288, AC002310, AL049548, AC006196, AC004491, AC005808, AC009479, AL022318, AC002350, AC006374, AC006449, AC004707, AC005296, AC010077, AF064861, AC002299, AC005393, AC005327, AC005668, AC003036, Z93241, AC006031, AC005783, AC005572, AL008720, AL031577, AL035458, AC004905, AP000510, AB023048, AC007015, AL118507, AF126403, AL031848, AC005015, AL031054, AL021407, AC006077, AL121578, AL049631, AF053356, AC003960, AC006359, AC002554, AC002451, AP000563, AC004813, AC008044, AC003103, AL008582, AC006597, AC004217, AC006505, AL008583, AC002559, AL121603, AL109829, AC007227, AC005875, AC016830, AF198098, AC007435, AL033533, AC006071, AL080317, Z99495, AL133321, AC006390, AJ239318, AL035695, AL049776, AC005187, AL024474, AC009247, AC006163, AC002300, AF023268, AL031120, AC006042, AC016027, AF130343, AC004934, Z83846, Z68289, AF111168, AC006132, AC004620, AC009731, AC006947, AC002429, AL122003, AL139054, AC006486, AC004838, AC006361, AC002470, AB016897, and AC004072.
HWLIG05	720	928226	1 - 384	15 - 398	AA055095.
HWLID27	721	682563	1 - 482	15 - 496	H01418, and AL109758.
HWLHW0	722	915161	1 - 530	15 - 544	AA923671, AI125697, and AC007239.

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HWLHU03	723	922931	1 - 522	15 - 536		AA078565, and AC005071.
HWLHK09	724	949288	1 - 777	15 - 791		AA740397, AI434125, AW136838, AA569863, AW105266, AI204298, W96043, AA716410, AI350484, AW290890, AW148513, AA447782, T53415, AI536855, T53416, R60197, AI984348, AI686362, AI248525, AW250847, AI992202, AI143894, AI992194, AI475478, AI805451, AI497917, AI131385, AI537372, AI138451, AW050818, AI188044, AI341988, AI092923, AI422529, AI470405, AI074107, AI761422, AI081852, AI240543, AA552656, AI741631, AA640107, W94806, AI709345, AI890651, AI741642, AA635765, AI000886, AA609560, R59720, AA279104, AA662394, AA960820, H43861, F26986, AI077909, AI266399, AW089381, AI022218, F33558, AW009700, AA454904, AA040893, W48641, N80191, AA029173, AA150947, D60131, AA018731, H08872, AI924093, N80837, H96895, AW408361, AA565574, AW090493, AW299693, AI799761, AI932812, AI800835, AI280339, AI798566, AA113310, T98488, AA161054, AW273622, AI653931, AI920904, AA720931, AA877404, AI276048, AI623560, C75200, AA654134, AI422772, AW134730, AW196781, AI583539, AI565141, AI689249, AA159367, AI800218, AI201482, T77050, AW193090, AI983710, AI306731, AI911743, AI346281, AI826240, AI312053, AA159139, AW193893, AW026429, AI955668, AW058431, AA150536, AI566956, AW264048, F09634, AI984335, AI031629, AA922838, AA983373, AI970021, W37151, AI610137, AI468182, AA828386, AI264211, AI023818, AA603941, T56771, AI659590, AA477573, AI050718, AA194496, AI701189, AI382466, H15148, AA565554, AI696419, AA159069, AW438920, AA496449, AA102717, AA248169, AA496515, AW024803, AW168713, AI955982, AW070799, AI244082, AI910614, AA526367, AA454830, W45378, AW129533, AW024804, AI766300, AA889374, N26161, AW176258, AW073374, AI362836, AA370818, and AL117551.
HWLHH62	725	876225	1 - 512	15 - 526		R76336, AI290972, AW082282, AI815098, AI935867, AI659188,

						AI421829, AA974182, AW276067, AI889106, AI625318, AI636809, AW079674, AI559518, HI2385, AI914585, AI342309, AI216199, AI336447, AI336445, AI476296, AA865622, AI301940, AI469758, AW251068, AI272699, AI832439, AW151910, AA573785, AI660665, AI333305, AI865986, AI688082, AA639087, D45438, R94963, C20912, AI908555, AA987621, H41084, AI590410, H70884, AI720940, H15022, AI274107, AA903732, AA935031, AW192993, AW132153, AI244423, AI199655, AI199654, AI832803, AA593195, AW269879, AA886276, AI110653, AI225252, AC006479, and AF115384.
HWLHD19	726	887203	1 - 618	15 - 632		U46349, AW392670, AL119355, Z99396, AW372827, AL119483, AL119401, AW363220, AW384394, AL119341, U46351, AL119418, AL119319, AL119457, AL119396, AL119324, AL119443, AL134536, AL119522, AL134902, AL119484, AL119363, AL119391, AL119497, AL042984, U46346, U46350, U46347, AL119444, AL119335, AL119496, AL134525, AL037205, AL042433, AI142131, U46341, AL119464, AR060234, AR066494, A81671, AR069079, AR054110, and AB026436.
HWLGV14	727	967914	1 - 441	15 - 455		R95048, H71284, AW250334, H39231, HI5021, AA309046, R45920, AI110653, AF115384, and AC006479.
HWLGA04	728	925682	1 - 560	15 - 574		AA805357, AW445088, AA457154, AA748596, and AA766556.
HWLFY91	729	789569	1 - 587	15 - 601		T55064, AL119418, AL119484, AL119483, AL079683, AC006480, AC005585, AC004966, AC004031, and AC007786.
HWLFY06	730	934635	1 - 651	15 - 665		AI828037, AI568552, AI911104, AI566345, AI768789, AA779329, AA693540, AA776299, and AW081695.
HWLFV52	731	950978	1 - 344	15 - 358		AA446725, and AW452377.
HWLFQ39	732	705200	1 - 861	15 - 875		R56641, R85020, T10207, R60097, Z43394, F11340, H28844, T66406, F06322, F12312, F11134, F05772, T80510, AI912281, AW419361, F06032, T06213, and AF070541.
HWLFM69	733	754644	1 - 547	15 - 561		AA236233, and AA253152.
HWLFH36	734	708387	1 - 396	15 - 410		AW025980, R63208, AW392670, U46347, AW384394, AL119484, AW363220, Z99396, AL119457, AW372827, AL119324, AL119319, AI043003, AL119497, AL119439,

						AL119391, AL119522, U46351, AL119363, AL119355, AL119443, AL119483, AL119341, U46350, U46341, AL119396, AL134528, U46349, AL119335, AL119496, AL119418, AL119444, AL037205, AL134530, AL134519, AL134531, AL119401, U46346, AL042614, AL134132, AL134533, AL043147, AL042984, AL042965, AL042975, AL042544, AL119399, AL134538, U46345, AL043033, AL043019, AL042542, AL043029, AL042450, AL042989, AL042551, AL134542, AL119464, AR066494, AR060234, A81671, AB026436, AR054110, AR023813, and AR069079.
HWLEFB71	735	759915	1 - 758	15 - 772		N99523, and AL035252.
HWLEZ11	736	966228	1 - 543	15 - 557		T50894, AI565243, and AW197960.
HWLEQ61	737	741224	1 - 502	15 - 516		R15994, Z39969, F04171, F03124, T40928, AI539854, AI146310, and T66620.
HWLEM80	738	886651	1 - 756	15 - 770		Z99396, AW392670, AW372827, AL038837, AW384394, AL119484, AL119391, AW363220, AL119497, AL037051, AL036725, AL119319, U46349, AL119483, AL119355, AL036418, AL119522, AL119457, AL119443, AL119324, AL119363, U46350, A4631969, AL039074, U46341, U46351, AL119341, AL119335, AL036858, AL119496, AL119396, AL119439, AL119444, AL119418, U46347, AL036924, AI142137, AL042614, U46346, AL037205, AL134524, AL042984, U46345, AL134538, AL134531, AL134542, AL042965, AL042975, AL038509, AL134528, AL119399, AL134518, AL043029, AL042544, AL037085, AI142132, AL037094, AL042551, AL043019, AL037526, AL043033, AL036196, AL043011, AL037639, AL036190, AL042450, AL042542, AL037082, AL036767, AL038520, AL037077, AL043003, AL036268, AL119464, AL036774, AL036998, AL038851, AL038447, AL036238, AL036733, AL037027, AL037178, AL037615, AL036719, AL036679, AL036765, AL036191, AL036886, AR060234, A81671, AR066494, AR023813, AR064707, AR069079, AB026436, and AR054110.
HWLEM01	739	915547	1 - 366	15 - 380		AI627456, AA935090, AA862195, AA761568, and AA886022.
HWLEL08	740	860161	1 - 675	15 - 689		AI799364, AI254420, AI572717, AI869403, AI799472,

AI811307, AI887247, AI831136, AA603709, AI244380, AW059713, AI802711, AI866741, AI631216, AI679959, AW242479, AI858310, AW104146, AI742026, AI691088, AI590787, AW079436, AI690946, AI589267, AI805638, AI499986, AI611743, AW083804, AA864406, AW265004, AI364788, AW152550, AI627988, AI648508, AW274355, AI890806, AI538764, AI696186, AI678762, AI073952, AA830821, AI683255, AI537735, AI874166, AI677797, AI554544, AI591412, AI285419, AI591081, AI536910, AI696626, AI864827, AI690449, AW088944, AW302924, AI624529, AI891157, AI679550, AW172723, AW193203, AI355277, AI040694, AI916419, AA829541, AW168503, AW084059, AW131999, AW088899, AI568138, AI288116, AI566630, AW263804, AI251830, AI289542, AW129271, AI867042, AI366549, AI636719, AW080205, W33163, AI446124, AI799650, AA983883, AI590423, AW090058, AI589993, AI678850, AI336575, AI537837, AW058233, R66759, AW193134, AI582871, AI963068, W46547, AI933992, AI632303, AI690312, AI433976, AW024889, AI288285, AI362637, AI473528, AI799657, AW403717, AA494167, AI046463, AI699255, AI677983, AI472536, AI288152, AI699011, AW161579, AI624668, AI564602, N74355, AW080214, AL036652, AW130863, AI783861, AW103371, AI921176, AI868831, AI950664, AW118414, AW021373, AI689420, AI678302, AI491710, AI368868, AI446605, AW409775, AW088144, AI540832, AI432040, AI280670, AI635464, AI040602, AI634450, AI539771, AI612843, AI567935, AI915576, AI857797, AI344928, AI537011, AI609594, AW131989, AI345737, AI345224, AI591074, AI619781, AI249946, AA760697, AI628324, AI432570, AW148621, AI345736, AI798258, AI539153, AI955906, AI553669, AI570966, AI336592, AL038575, AI890057, AW073697, AI874351, AI929108, AI620093, AW118373, AI311892, AI873638, AI567978, AI886055, AA908294, AI590761, AI292249, AI811845, AI912288, AI302559,					
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AI590645, AI889839, AI888482, AI752007, AI805688, AI872159, AI344933, AW103228, AI038529, AI862324, AI886594, AI365256, AI669639, AI866082, AI148272, AI470293, AA806719, AI687568, AI866994, AI591057, AW192288, AI473598, AW085786, AW151847, AI250627, AI863256, AI446373, AI471662, AW090103, AI349933, AI573026, AW148716, AI307736, AI866608, AW268261, AW073898, AI436429, AI473451, AI306706, AW082532, AI537677, AW084097, AI249877, AI873644, AI872300, AI263584, AI609677, AI888621, AI612759, AI357599, AI539800, AI679179, AW104141, AI865320, AI242736, AI345253, AA848053, AW149876, AW079334, AI040241, AW089006, AW087938, AI289310, AI345677, AI500523, AI623682, AI560679, AW073699, AI8777, S77771, A93016, AL137556, I48978, S79832, AF022363, AF132676, AF061836, AL137555, I89947, A08913, AF036941, I89931, AL122106, A08912, A08910, I49625, A08909, E15569, AR038854, AL133093, A08908, S76508, I89934, A08916, AC002467, X72387, AF106862, E15582, X93495, AL122123, AF118070, AL122050, I66342, U51587, AF078844, AL049938, I26207, AB025103, AF030513, X56039, AL133098, AL049452, S69510, A57389, AL137526, U92068, U95114, X55446, U96683, S68736, AF106657, AF182215, D83989, I89944, AR019470, AF143957, AL110221, A90832, AL117440, AL122118, AL049465, AL137537, AL133104, A08907, AF114170, AF118064, AR038969, AF051325, AL133645, AL122111, Z82022, AJ238278, X92070, AF017152, AL117578, AL122045, AL133077, AB029065, X53587, AL137539, AR034830, I96214, I09360, AL049460, U90884, I42402, AL110197, I17544, AL133557, AL080158, AL080127, AL133568, AL133014, AF185576, AF180525, AL117432, X96540, I22272, AL137276, I41145, E03348, X06146, AF065135, E03349, AF107847, AL133624, AR059958, AL117629, AL137294, U77594, X65873, AL133665, E02221, L04504, U72620, A58524, A58523, AL137300, AF111112, Y10080, AL080060, AF067790,				
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					AF012536, AL137429, AL133067, Y16258, Y16257, E02756, Y16256, AL137557, X87582, E05822, AL110196, AR000496, U39656, AL117626, AL137538, X84990, X59414, AF090886, AL137712, A45787, AL137495, AL080137, AL137705, AL137527, AL133619, AL050138, AF137367, X62773, AF000145, AJ012755, M92439, S78214, A18788, AC004686, X81464, U75932, S75997, AF113019, I48979, AF090934, Y16645, U67958, AF118090, AL080154, AF210052, AL110296, AF183393, AF153205, AF159615, AL117585, AL117649, AL137711, E07108, U87620, AF090903, AF125949, AL137488, AF032666, D83032, A08911, AF162270, E02152, AF207750, AL133637, AF100931, AL122049, AL080074, AL133081, U58996, AL096744, AL137547, AL050393, AL133606, Y08769, AL050277, AL117583, L13297, AF118092, AF026030, U00686, AF040751, A27171, AF016047, AL137463, AF169154, U00763, S61953, AL080086, AF119337, I18355, AF118094, X79812, I34392, E02253, U75370, AL133640, X80340, Z72491, X52128, AL049466, AF094480, AL122098, AB007812, J05032, U42031, AF113676, AF158248, U49434, AL137658, AF146568, U80742, U72621, AL133113, AL050092, X57961, AL133565, AF008439, AF081197, AF081195, AF002985, A21103, AL122110, AF028823, S78453, AF113689, and L19437.
HWLEK75	741	766928	1 - 621	15 - 635	AA191612, H46176, AI479578, T79613, AI936360, and AC006006.
HWLEI57	742	734267	1 - 455	15 - 469	AL041375, AA557945, AA911515, AA053463, AI310992, AI300818, AI250552, AI251034, AI254770, AI284543, AI054090, AA503019, AA206707, AI251284, AI251203, AI249853, AL044701, AI623364, AA788592, AA630535, F17537, AW303098, TS4783, AA493808, AI135761, AA736713, AW084004, H27165, AI572680, AA364082, N49298, AW276678, AA480486, AA580251, AA469230, AA832016, AI524193, Z84474, AC004883, AC000353, AC007664, AL121693, AC005821, U78027, AJ246003, AL109627, AL132712, AC007308, AF053356, AC005225, AL031681, AP000694, AC007371, AL031848, AC006211, AC004797, AC005280,



AC002310, AC005015, AC005755, U95740, AC005902, AL049538, AC005736, AC005696, AF129756, AC002470, AC005913, AC004019, AC005670, AC006966, AL133245, AF109907, AC006285, AL035681, AL049780, AL121757, AC005519, AF030453, AC006449, AC007055, AL121655, AC006126, AC004144, AL021707, AC004975, AL096701, Z84469, U85195, AC007227, AL035422, AL035684, AC000026, AF165926, AC005527, AC004813, AL133448, AC004099, AL009181, AC005089, AB003151, AC003029, AC004814, AC005695, AL050341, AL031255, AC005940, AC004477, AL034417, AL034347, AE000658, AL020995, AC002059, AC004686, AC016027, AC020663, AC005049, AC002492, AC016830, AP000501, AC007216, AC004526, AF181896, AC006511, AC005694, AL022726, AC004878, AL022326, AL031295, AC004491, AC006450, AL139054, AC005288, U62293, AC006396, AC006487, AC000159, AC004967, AC005412, AP000030, L78833, AP000116, AC007151, AL109801, AC005041, AL022336, AC005375, AC004816, AP000555, AC018633, AC004983, AL031767, AC005529, AL050318, AL078476, AC002477, AF205588, AP000212, AP000134, AL122020, AL121754, AC005057, AL031133, AL022320, Z83844, AL031311, AC007688, Z98047, AC000111, AL031659, U80017, AC016025, AC004079, AL049631, AL031733, AL022165, AL035458, AC005823, AC000120, AL008719, AL031673, AL024498, AC006480, AL049697, AC004890, AL049776, AL022323, Z95113, AC006115, AL035398, AC002316, AC002544, AC005808, AF001549, L44140, AL109758, U47924, AC006057, Z99716, AC007536, AC005399, AC007406, AJ003147, AC005740, AC004098, AC004938, AC004263, AL133353, AL033392, AC004448, AC005899, AB016897, AC006111, AC004150, AC007917, AC005261, AC006116, AL034420, AL117337, AP000245, AP001053, Z94056, AP000553, AC006538, AC005531, AC007225, AL031431, AF111168, AC004659, AC005971, AL049743, AC006597, AC006312, AC006441, AC004149,

						AFI96969, AC005697, AFI34726, AI034549, AC006023, AP000503, AC007537, and AC007546.
HWLEH70	743	874721	1 - 590	15 - 604		W95010, AW374112, AA040829, AA836635, AA970717, AA314614, AA452356, AA476400, AW024516, AW129435, AI092491, AW072060, AI189134, AI150134, AA699453, AI263271, AA761739, AA703279, AA777528, AI342713, AA872292, AA843158, AI306603, AA844071, AI313465, AI301275, AA700663, AI032928, AA694526, AI040112, AA029630, AI802249, AI199009, AA776987, AA603711, AI720350, AA581863, AA034078, H68850, AA001365, N29685, AA092097, N89776, AA453539, AA775544, T62617, AI365084, AA877094, W52538, AA612919, AA029629, AW178377, T78021, R99078, AI080297, AA004832, AI620227, H01073, AI216849, N27222, AA039446, W01129, AI310514, H83755, AA380107, AI051240, AA361143, AA115074, AI290791, AI859418, AI859411, AI986177, AI084639, AA039371, AA777506, AA507629, AI675135, AI886105, W17298, AA887931, AA702656, AA232398, N56695, N56643, AI042295, AA173895, AA173539, AI458814, R99621, AA769877, H04197, N89377, W93148, AA824483, AI858388, AW070969, AA352755, AA677474, AA808719, AA516411, AI493901, AI478868, AI034012, AI340978, AI688193, AI128512, N30311, AA814454, AI969239, AW169015, AI090574, AA873007, AI079514, N52956, AA452133, AA937208, and AA465533.
HWLEF27	744	682572	1 - 256	15 - 270		RI3584, and AB011117.
HWLEA48	745	927676	1 - 415	15 - 429		AAI30828, AFI69034, Z98752, and AFI69033.
HWLDX03	746	922806	1 - 568	15 - 582		ALI133990, AI829770, AA505700, and AI128582.
HWLDB04	747	887051	1 - 493	15 - 507		AW117683.
HWLCM06	748	934117	1 - 459	15 - 473		AI818839, and AA557932.
HWLCG42	749	975246	1 - 672	15 - 686		AW075378, ALI19483, ALI19444, ALI19484, AC006101, and U91323.
HWLCD10	750	974071	1 - 473	15 - 487		AW392670, U46347, AL043003, Z99396, ALI19457, ALI34528, AW363220, AW384394, AL043033, U46351, ALI19324, ALI19444, ALI19363, ALI34533, ALI34531, ALI19497, AI142132, AI043147, ALI34132, AL042450, AR054110, and

HWLBO06	751	934630	1 - 306	15 - 320	AR066494. AI628414, AW190183, AA505080, C21450, AA629929, and AA725256.
HWLBN90	752	787355	1 - 597	15 - 611	AA194905, AA164603, and AF155115.
HWLBL75	753	766877	1 - 634	15 - 648	AW005748, AA923548, AA287724, AA046075, AA280716, AI215902, AA579688, N94002, AA046023, AI766599, AA740808, T92453, AA287725, T91495, AI540782, AA489673, AA281431, AW172264, AW419052, AC005667, and AC005206.
HWLBI01	754	919168	1 - 329	15 - 343	T84925, AI453533, AA662451, AI797910, AI863269, W49529, AA969280, AA909645, AW016106, AA704629, AI217567, AA253458, AI583564, AI268910, AI261516, AI223214, AI080077, W49530, AW452178, AI423758, AI685699, AW264194, AI424097, AI494222, AA161335, AA861082, AI359963, AI278825, AI087203, AI292023, AI348189, AI422074, AI356252, AI700817, AW003844, AA833762, AA437126, AA765993, W56681, AI240846, AI933190, AA777656, and AF053356.
HWLAU04	755	953433	1 - 277	15 - 291	AI014455, AI816843, AI934427, AW207409, AA594108, AW439577, AI921123, AI818217, AW301697, AI128260, AW270896, AW243099, AI923407, AI304364, R44786, AI269569, AI022996, AI962499, AW205076, AA860774, AI023565, AI675320, AW236056, AA846210, H20525, AL043236, AA189144, AW188621, AA398933, AI682364, AI869776, AI972233, AI436782, AI097649, AA492565, AW194337, AW337725, AW150303, AI911832, AI783975, AA427732, AA976448, AI423327, AA705924, AA122228, AI933805, AA029379, AI272795, AW276106, AI049990, AI679079, AA678767, AI863602, AW235480, AA610003, AI307297, AI401790, AA426384, AW339352, AI832158, W61155, AA299998, R50517, AI766939, AW237533, AW292612, AI800262, R56910, AI480367, R62414, AI363258, AI880530, AW237296, AA434297, N75586, F09963, R80409, AW242309, AW051761, H84210, T81795, W61203, AI872364, AA029378, AA121106, R62413, W07269, AI695106, T72570, N79770, AI142598, AA910677, T82115, AF105365, and

HWLAQ11	756	966207	1 - 554	15 - 568	AL117433.
HWLAL10	757	971666	1 - 438	15 - 452	AI801975, AI698139, AI681600, and T24770.
HWLAC70	758	775771	1 - 428	15 - 442	AI453678.
					AI983434, AW341645, R86046, AI370387, AI582925, AA860287, AA931253, AW242845, AI355711, AI003805, AI674918, AI953136, AI439138, N30181, W74524, AI342466, N48608, AI203795, AA406573, AI916617, AI433905, AI590313, R77949, AI565402, AA411759, AW242806, AI918584, AI263073, and AI375289.
HWLAC29	759	690263	1 - 363	15 - 377	AI200957, AI371025, AI362183, AA765552, AW058085, AW134520, AI635734, R91403, H68404, AA648201, R02100, and AI494370.
HWLAB74	760	765196	1 - 522	15 - 536	H23551, AI376191, AI129920, AI424576, AA478517, H23995, HI0292, HI0851, and HI0852.
HWGQA42	761	713348	1 - 350	15 - 364	H25446, and AC006353.
HWCAG11	762	966623	1 - 747	15 - 761	AI973037, AA760709, AW072412, AI969836, AI201581, AI824062, AA827147, W56389, W37398, AA490346, AI042370, AI221443, N98734, AW419070, AI216467, AW439942, AW206961, AI279656, AA643010, AI341522, AW073983, H83782, AA769021, AI202559, W31174, and H83925.
HWCAD06	763	886808	1 - 689	15 - 703	AI134524, AI393398, AI142134, AI038983, AI037727, AI045328, AI049018, AI039643, AI134110, AI038838, AI037343, AI037436, AI037335, AI037323, AI037443, AI038532, AI038822, AI039432, AI044125, AI041347, AI040193, AI037435, AI043923, AI043814, AI047012, AI044162, AI041238, AI044186, AI040617, AI043845, AI043496, AI045753, AI047163, AI040463, AI047170, AI044037, AI041635, AI040294, AI044064, AI041459, AI041577, AI038761, AI047219, AI040576, AI040625, AI043538, AI040621, AI045684, AI040472, AI041752, AI046850, AI040768, AI046994, AI046914, AI046442, AI040052, AI040444, AI040464, AI040510, AI043467, AI043677, AI040839, AI043492, AI041602, AI044074, AI041730, AI041523, AI043627, AI041374, AI047183, AI043848, AI043570, AI042135, AI041955, AI041324,

				AL041133, AL045671, AL039360, AL041098, AL045327, AL039316, AL040322, AL042898, AL046392, AL040119, AL044272, AI547295, AL044258, AL045990, AL042096, AL041168, AL041163, AL041159, AL037295, AL045920, AL040148, AL047057, AL041296, AL037341, AL040458, AL044187, AL038745, AL044274, AL041358, AL041086, AL041292, AL040571, AL041346, AL041142, AL040332, AW392670, AL039338, AL079878, AL040529, AL041233, AL041197, AL037279, AL046330, AL040745, AL040370, AL040128, AL040553, AL047036, AL040342, AL041186, AL040414, AL043941, Z99396, AW372827, AL038651, AL039744, D29033, AL041277, AL040285, AL119324, AL040155, AL040091, AL044165, AL041131, AL040090, AL079852, AL048677, AL041051, AL040168, AL038878, AL043775, AL040253, AL045857, AL038837, AI318479, AL037051, AL036725, AL036418, AA631969, AL039074, AL045817, U46347, U46344, AL039085, AL039564, AL036858, AL039156, AL039108, AL038509, AL039109, AL039128, AL036924, AW384394, AW363220, AL119484, AL037094, AL048714, AL039659, AL135012, AL038531, AL036196, AL119443, AW363350, AL039625, AL039648, AL048657, AL045337, AL036767, AL038024, AL119457, AL037082, AL043003, AL037526, AL036190, AL038447, AL119497, AL037639, AL119319, AL039678, AL039629, AL039423, AL041344, AL036238, AL039150, AL119439, AL045494, AL119391, U46350, AL040992, U46351, AL042909, AL119522, AL042523, AL038520, AL119483, AL119363, AL119418, AL119355, AL037077, U46341, U46349, AL119341, AL119396, AL037726, AR066494, AR064707, AR023813, AJ238010, AR060234, D17247, A93923, A93916, A81671, AR069079, A93931, A85203, AB026436, AR054110, AL133053, AL122101, AL133074, and AL133049.
HVATY05	764	928713	1 - 671	15 - 685
HVASJ79	765	951617	1 - 1632	15 - 1646

						AW268779, AA653972, W22172, AA502940, AA554515, AI492218, AW304606, AI743201, AI198344, W87734, AI041005, AA369185, W87696, W87733, AI085432, AI051262, AW044590, AW051567, AI089831, T48516, AA780298, AA235536, AA410617, AI821566, AW149849, AI677815, AI687568, AW059713, AI370322, AI440444, AW409874, AI654135, AI117585, A51774, AF081571, AF114818, X56530, AI133081, U68233, I92592, D25291, X95876, AI133077, AI022165, AF043345, L10613, and D82790.
HVAPI01	766	913930	1 - 759	15 - 773		AI347604.
HVAET01	767	913958	1 - 426	15 - 440		AI299187, and AI133243.
HVAEP04	768	925914	1 - 290	15 - 304		AI811989, AI570961, Z99396, AW392670, AW363220, AW384394, AW372827, AI119443, AI134902, U46349, AI119396, AI119341, AI042965, AI119497, AI119319, AI134527, AI119457, AI119483, AI119324, AI134518, U46351, AI119484, AI119363, AI119391, AI119355, U46350, AI134920, AI119399, AI134533, AI134528, AI134538, AI134524, AI119335, U46341, U46346, U46347, AI134536, AI119444, AI119522, AI037205, AI134529, AI119439, AI042433, AI119418, AI080317, AR060234, AR066494, A81671, AR069079, AR054110, and AB026436.
HVACY04	769	926473	1 - 449	15 - 463		H05055, T63507, and AI611300.
HUTSF11	770	966029	1 - 416	15 - 430		AI384010, AI288640, Z20435, and A74523.
HUTAF08	771	958353	1 - 467	15 - 481		AA977579, AA421364, AA815356, and H95526.
HUFGC48	772	950707	1 - 429	15 - 443		AA458691, AW242885, and AC004988.
HUFFW06	773	934895	1 - 568	15 - 582		AA027335, AA081555, AI872625, AI799533, AC005050, AI096791, AC004755, AC002425, AC002470, AC007308, AF053356, AC007207, AC005015, Z85996, AJ011930, AC007993, AC016025, AC004019, and AC005520.
HUFFC02	774	969054	1 - 367	15 - 381		AA065154, AA065155, AI183935, AW301116, AW057873, AA403324, AF147446, and D80010.
HUFDO11	775	966407	1 - 404	15 - 418		W03945, AI884522, AI355246, AI041375, F35684, R67701, AA834816, AW089016, AI573009, AI039257, AI801649, AW021674, AA338238, AI126969, AA809546, AA582746, T57096, AI445373, AW242031, AI804539, AA568204,

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HUFDN22	776	783765	1 - 430	15 - 444	AA233997, AL135608, AA157308, AI934999, D81149, D60727, AI969520, H23082, W22896, F07060, AA299769, AI749069, AI829619, AW006228, AA299827, AI354690, AA773322, AA480943, AI494218, AA643671, AI343102, and AF071172.
HUFDH29	777	689979	1 - 707	15 - 721	H14683, R56199, AI686422, T74277, F12415, T68970, R12972, Z42675, and AB023201.
HUFD803	778	923561	1 - 531	15 - 545	N31538, N31041, and N44826.
HUFCO89	779	786817	1 - 299	15 - 313	
HUFCO04	780	731462	1 - 358	15 - 372	AA743394.
HUFCI80	781	773161	1 - 808	15 - 822	AA075994, W63643, AA043571, AW376194, AA348642, AA578387, H10706, AA081648, AA852140, AA332535, D82793, N56274, AA384733, T27278, AA057498, AA094783, Z19471, AA174144, AA305150, AC005838, AF151906, U91322, AC003065, AC005033, AC006543, AC006544, and AR019365.
HUFBP22	782	582067	1 - 496	15 - 510	U86136.



HUFBD16	783	661856	1 - 452	15 - 466	H79879, R97868, AC006312, AL109628, AC007731, AC005500, AF205588, AF139813, AC004228, AL031311, AF001549, AL121603, AL050338, AL049776, AC005261, AF003529, AP000512, AC005562, AC002377, AB023051, AC007298, AL050348, AC005971, AC006241, AC004694, AC006130, AC009247, AC007011, AC004834, AC005529, AC007225, AC004994, AF196779, AL021393, AL049643, AC005527, AC005399, AC007308, M89651, AC004938, AC006511, AC006084, U47924, AC005015, AC005207, AL096701, Z93023, AC004019, AC006515, AC002470, AF111167, AC006211, AC004081, Z84484, AC004832, AC005531, AC004686, AL035420, AL132777, AC003071, AC002400, AC005695, AC006017, AC005274, AC005519, AC004975, AL031680, AC004000, AL022476, AC006512, AL031848, AC008044, AC002091, AL034379, AC004820, AL035685, AC003098, AL121825, AC006077, AL133485, AL139054, AC003029, AL031575, AC007686, AC004922, AC004531, AC007450, AC005089, and AP000503.
HUFAU90	784	787302	1 - 477	15 - 491	N47541, and AL122084.
HUFAO77	785	772133	1 - 288	15 - 302	H10059, and AC004016.
HUFAO24	786	467860	1 - 576	15 - 590	W48600, and AL117454.
HUFAJ16	787	621443	1 - 743	15 - 757	AI538273, AI027279, H92221, AA806405, AI061158, AA225519, AA505108, AI446618, AA765899, AI884404, C18748, H86399, AI567676, AW022796, C75332, AI571094, AI801479, AA364082, AW157128, AW028376, AI554399, AI031759, AI281622, H53546, AI805699, AI570067, AI000314, AI434103, AA873661, AW029626, R79396, AI798521, AI038029, AW085626, AA772818, H47461, AI860648, AI251024, AA809104, AI821945, AW338633, AI307563, N72678, AI708565, AI921744, AA569220, AA635150, AA411337, AW104040, AA349923, H24331, AA171400, H05066, AA935827, AA218684, AI888050, AA084320, F31670, AA604601, AI869886, AI890283, R61887, AI174703, AA714190, AI114755, AA143703, AI572680, AA293809, AA083850, AL041375, AA084148, AA618531, AW148974, AA152398,

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HUFAG52	788	727087	1 - 307	15 - 321	AW291225, AI261702, R38814, AI186145, AA905337, AA863136, AI221372, AI271720, AI279205, AA894648, H88964, D61989, AA251615, and AF070595.
HUFAB12	789	970725	1 - 589	15 - 603	AI738566, AI278276, AI493198, AI198274, AI143511, and N26559.
HTPHG02	790	918237	1 - 896	15 - 910	AA203149, R00127, and AL044506.

HTPFS02	791	918251	1 - 277	15 - 291	T61298, and AI.049839.
HTPFF82	792	869864	1 - 448	15 - 462	
HTPFF81	793	869862	1 - 369	15 - 383	
HTPEI73	794	465462	1 - 317	15 - 331	AA279040.
HTPDZ79	795	968067	1 - 1222	15 - 1236	F12986, H53276, AA037611, T75365, T75366, F12985, R34645, AA249802, AI989482, and AW296784.
HTPDV49	796	931787	1 - 2594	15 - 2608	AC003031.
HTPDA96	797	796101	1 - 457	15 - 471	AW006814, AW003336, N48824, and AW136088.
HTPCZ41	798	576943	1 - 756	15 - 770	AI732452, AA088857, AI732595, AW351701, AI424922, AA132858, AW375352, AA149682, AI733889, AI132946, AI420906, and AW362901.
HTPCV43	799	459467	1 - 447	15 - 461	H27024, AI128444, and AI346860.
HTPCS79	800	835550	1 - 376	15 - 390	H38451, H52133, R87761, R87771, AI922949, AI922958, AI972432, AI961967, AA568658, AW009248, H18285, H43455, H61275, and AI.022328.
HTPCR30	801	574757	1 - 359	15 - 373	AA604872, H49701, and AC004087.
HTPCE41	802	712642	1 - 498	15 - 512	AA259015.
HTPBX04	803	927828	1 - 471	15 - 485	R56356, and Z45031.
HTPB39	804	530441	1 - 162	15 - 176	
HTPB35	805	530440	1 - 352	15 - 366	AI870357, AI935062, AI285992, AA251405, AA287379, AA826944, AA621133, AI831481, AI244734, AA806652, AW103288, W73663, AW182748, AI244664, AA436810, AI422961, AI246681, AA701034, AA969674, and AF109377.
HTPBD55	806	754147	1 - 306	15 - 320	AA135370, W84729, AA295630, and R01600.
HTPAT20	807	668771	1 - 388	15 - 402	T54340, AA295321, AL133289, and AB007895.
HTPAF93	808	791415	1 - 220	15 - 234	T39933, and AA295307.
HTPAO01	809	961062	1 - 590	15 - 604	AI949455, AW303582, AI223408, AA625586, AA416613, AI016819, AA416708, AI192010, AI126130, AI139838, AA295198, and H88336.
HTPAI20	810	937644	1 - 406	15 - 420	AA294985, and AI380819.
HTPAG06	811	960784	1 - 557	15 - 571	AA456950, and AA386216.
HTPAE77	812	772737	1 - 520	15 - 534	AA075738, and AA386160.
HTNTA60	813	840258	1 - 498	15 - 512	AA158012, and AA158013.
HTNGF71	814	870037	1 - 356	15 - 370	AI922002, AA084725, AA189117, T90474, AI.022313,

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HSPMF55	815	871310	1 - 259	15 - 273			N53881.
HSPMF20	816	575826	1 - 89	15 - 103			
HSPBD58	817	735472	1 - 513	15 - 527			AI819387, AW088020, and N23867.
HSPBC71	818	759886	1 - 969	15 - 983			N67323, AW080010, H88870, H88869, R67715, R99014, H88812, AI467915, AI038309, and AI039030.
HSPAY58	819	964178	1 - 522	15 - 536			AW269831, AA978290, H55860, H55768, C17251, AA236378, and AL035249.
HSPA156	820	582583	1 - 425	15 - 439			R23560, and AC004099.
HSPA152	821	727212	1 - 383	15 - 397			R13857, and AB023157.
HSPAB58	822	736098	1 - 347	15 - 361			AI718112, AA702244, and H64345.
HSODZ52	823	825096	1 - 290	15 - 304			H79244.
HSODZ07	824	955932	1 - 493	15 - 507			AA157075, AW188258, AA931237, AI270586, AI133526, AA594603, and AA133527.
HSODV84	825	782529	1 - 687	15 - 701			AA053854, W96253, and AA017300.
HSODU86	826	784754	1 - 482	15 - 496			AI968592, N67733, N28526, and W03579.
HSODS38	827	709399	1 - 377	15 - 391			N33966.
HSODR06	828	934645	1 - 610	15 - 624			AA181481, and AA179806.
HSODK89	829	786581	1 - 415	15 - 429			R24235.
HSODH33	830	701833	1 - 617	15 - 631			N77561, and AI992358.
HSODE10	831	963727	1 - 636	15 - 650			AA234172, AA687622, AI015113, AA716277, AI803384, AW022936, AI769040, and AW023108.
HSODD28	832	685884	1 - 602	15 - 616			H12860, and AI457605.
HSOBR45	833	717282	1 - 611	15 - 625			W92082.
HSOBP04	834	871340	1 - 421	15 - 435			AA806268, and AA115758.
HSOBO01	835	882825	1 - 316	15 - 330			H55784.
HSOBN03	836	923315	1 - 658	15 - 672			AI084492, and AA449407.
HSOBM53	837	727811	1 - 453	15 - 467			W87318, and AL022725.
HSOBK75	838	766940	1 - 576	15 - 590			N56958.
HSOBA75	839	766949	1 - 422	15 - 436			H00767, AI971202, C20774, and AJ006945.

HSOBH84	840	782118	1 - 320	15 - 334	H30159.
HSOBF30	841	691440	1 - 540	15 - 554	N21031, AI476774, AI095242, AI690069, AI735444, AI591041, AI129276, AI219905, N81051, AW236759, AI148241, AI689543, AI867483, AA815339, and AA653637.
HSOBE61	842	908598	1 - 479	15 - 493	AI280287, AA309966, and AC012627.
HSOBE03	843	923322	1 - 373	15 - 387	AI681558, AI871606, AA411144, AI732390, AA493545, AA578271, AA551639, AA507763, and AI702844.
HSOBC07	844	952409	1 - 603	15 - 617	AA776312.
HSOBB11	845	966281	1 - 213	15 - 227	AI391598, AI037447, and W03972.
HSOAV63	846	745328	1 - 336	15 - 350	T99715, and T67265.
HSOAV11	847	967590	1 - 502	15 - 516	AI681455.
HSOAO64	848	746993	1 - 320	15 - 334	AA947294, AA579887, AW195781, R63652, and AI049610.
HSOAM10	849	968316	1 - 357	15 - 371	AA186347.
HSOAM07	850	953954	1 - 373	15 - 387	AI017267, and AI719772.
HSOAI35	851	537540	1 - 414	15 - 428	R40859, AA995479, AI048244, AI048243, AC006599, and AB018333.
HSOAG31	852	698357	1 - 294	15 - 308	N53108, and AF179633.
HSOAF76	853	877300	1 - 314	15 - 328	AA002207, R73816, R73841, T94384, AA225376, AA226684, AA225124, and AA225347.
HSIGL32	854	698756	1 - 194	15 - 208	T76945, R20210, and AC002996.
HSIGK77	855	771815	1 - 462	15 - 476	T71734, H90094, and H90004.
HSIGK64	856	746241	1 - 408	15 - 422	R25019, and R13488.
HSIGJ94	857	793624	1 - 643	15 - 657	AI984175, AA171807, AA262226, and AA127254.
HSIGG54	858	887545	1 - 449	15 - 463	AF015416.
HSIGG42	859	713339	1 - 382	15 - 396	H30811.
HSIGF42	860	866561	1 - 495	15 - 509	Z42388.
HSIGD15	861	659718	1 - 458	15 - 472	T88827, AI248440, R10334, and AC005534.
HSIGA25	862	677668	1 - 526	15 - 540	AA428755, and AI245055.
HSIFZ27	863	682580	1 - 252	15 - 266	H68353.
HSIFY57	864	734373	1 - 929	15 - 943	R34025, H06626, and AI536612.
HSIFV93	865	792005	1 - 516	15 - 530	N34941.
HSIFV59	866	786436	1 - 475	15 - 489	T57378, and AF072825.
HSIFR52	867	726370	1 - 510	15 - 524	N50768, and AA210990.
HSIFL30	868	691630	1 - 339	15 - 353	H90238, and U51561.

HSIFK84	869	782810	1 - 544	15 - 558	W21172, AI298234, AA019846, C15076, D59317, D80164, D59551, D59695, D59627, AI535686, D59503, D59502, Z21582, AA305409, Z30160, AA305578, D52291, D59275, AI535665, D31458, AI525923, AI525925, AF050070, AF050079, U19859, AF050069, AR060385, AB002449, A82595, I79511, A84916, AB028859, and AJ132110.
HSIFH19	870	668188	1 - 425	15 - 439	N94164.
HSIFD30	871	691636	1 - 442	15 - 456	AA116123, AA455933, AI277496, AW173279, AA479355, AA766385, H89964, AI807026, AA962459, AW270945, M85836, and AW138978.
HSIED64	872	747012	1 - 528	15 - 542	AA024953, AI130858, and AW024581.
HSIED52	873	726017	1 - 546	15 - 560	AA010315, AA887112, AI278227, AA010314, AI143410, AA040265, AW204117, AA694360, AI760943, and AI375956.
HSIEA68	874	753612	1 - 587	15 - 601	AA005148, R10757, and AC005940.
HSIDZ18	875	666892	1 - 282	15 - 296	AA133985.
HSIDU10	876	866596	1 - 881	15 - 895	
HSIDS63	877	745340	1 - 309	15 - 323	T73745, AW016390, AI471124, T73755, AI419108, AW026357, AI419596, and AI366515.
HSIDQ95	878	795033	1 - 480	15 - 494	W73818, W73851, R08292, and AI347540.
HSIDH25	879	679296	1 - 396	15 - 410	R15266, AI047469, and R05647.
HSIDD63	880	559788	1 - 548	15 - 562	T47922, AI671768, AW207720, AA701250, AW271763, AA702739, AI985183, H66133, H66549, W73428, AW372345, W69666, AW294792, AW292636, R19745, AI081094, AW292633, AI478491, W73367, AW089880, R84393, AA976621, AA704633, and AC020663.
HSIDC85	881	783403	1 - 605	15 - 619	W78843, and AI109659.
HSIDB51	882	725888	1 - 443	15 - 457	T83064, AC002094, Z69908, AC002324, and AB011096.
HSIDA48	883	721885	1 - 157	15 - 171	T66036, T65877, and AC004099.
HSICV38	884	827957	1 - 559	15 - 573	AA425507.
HSICU58	885	507172	1 - 349	15 - 363	AI078644.
HSICQ22	886	675004	1 - 478	15 - 492	T77227, AW058031, T99440, AA373896, T82852, N27680, AA533883, AA057865, AI121653, AA056931, and AI041059.
HSICP86	887	785733	1 - 325	15 - 339	T81910, and T91158.
HSICP22	888	586284	1 - 313	15 - 327	AW062662, AW177873, AW178142, AW178143, AW178141,

						AW178144, AW177807, AW177808, AW062663, AW062664, AW178173, AW178226, AW178225, AW062666, AW178146, AW178110, AC005041, and AC006544.
HSIBB22	889	518673	1 - 276	15 - 290		AA298647, AA377325, AA338289, AI276360, AA558404, AA456149, AW023111, AI358712, AW265126, AA610255, T06805, AW265688, AI310464, AA533054, AI590442, AI053673, AI572680, AA298573, F31654, AI249365, F26072, T50490, F31951, AI820534, AI821382, AI628859, AI587467, AA523695, AA180775, AA483483, AI870453, R93919, AA482928, AA502110, AW150387, AI583532, R91030, AI287921, AI769271, AC004832, AL117337, AL135960, AJ131016, AC007676, AC004967, AL133245, D00591, AF205588, AC004883, AC005288, AC005399, Z84487, AC005102, Z85986, AL020997, AC007055, AL050341, AC007684, AC006344, U91323, AL034418, AL035457, AP000556, AP000347, AC004112, AC005538, AC003963, AC005516, AC006120, AC007731, AL139054, AC005500, AC004531, AC000091, AC006057, AL031178, AC007690, AF053356, Z98884, AC002316, AC005839, AC002492, AF165926, AC005180, AL133448, AL109628, AC005484, AL078581, AC022517, AC004019, AC004983, AF111168, AP000355, AP000087, AC007052, AF129756, AP000272, AL121655, AL022476, AC006001, AC005619, AC005914, AC006050, AD000091, AC005358, AL133163, AB017602, AL022320, AC005015, AC004559, Z95115, AP000226, AC004084, AC006146, AP001068, AP000104, AL096791, AC003043, AL049776, AC003101, AC007899, AJ011930, AL049694, AC005921, AC005280, AC005837, AC007201, AP000688, AP000032, AC004991, AC005229, AB003151, AL032821, AC005225, Z97632, AF067844, AC003007, AF196779, AC007226, AC005081, AL034429, AF107258, AC005777, AC002544, AC007537, AC004647, AP000692, AC005013, Z98941, AL021918, U85195, AP000031, AC007566, AL109865, AC005274, AB023048, AC007065, AC006312, AP000343, AC006285, AL031846, AC004706, AL135744,



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HSIAQ22	890	505052	1 - 351	15 - 365	AL118900, AP000535, AP000079, Z81144, Z98751, AC000003, AC004033, AC007536, and AL035072.
HSIAL16	891	496026	1 - 660	15 - 674	R07186, AA563825, R07178, F35011, AL048969, AA601230, AI144081, AW302711, AL127426, AI753092, AW302753, AW085751, AA169245, AA515048, AA679625, AA501906, AI675615, AW301906, AI282253, AA693366, AI049709, AW338021, AI053560, AI133727, AA015948, AA654484, AW268300, AA719732, AP000501, AP000240, AC004884, AC004832, AC005280, AC007298, AP000030, Z84469, AC005089, AL022323, Z97053, AC004167, AC007226, AC000353, AC004963, AP000502, AC000025, AF111168, AC007371, AL080243, AL022302, AF190465, L44140, AL132712, AF196779, AC005412, AC005409, AL049874, AC005088, AC003072, AC006449, AL020997, AL121655, AC007421, AC002073, AB001523, AC005971, AC005081,

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HSIAI62	892	522231	1 - 354	15 - 368		
HSIAI37	893	698015	1 - 61	15 - 75		
HSIAI03	894	960907	1 - 720	15 - 734		AI346656, AI346667, and AI380663.
HSIADI1	895	964915	1 - 424	15 - 438		AA376854, and H02592.
HSIAB63	896	745637	1 - 523	15 - 537		AA196018, AA775199, AA706922, AI798729, AA132243, AA132242, AA192334, AA973154, AA376742, and AL049709.
HSIAB05	897	932922	1 - 497	15 - 511		AA127651, and AA376726.
HSCBB01	898	916772	1 - 410	15 - 424		AA781220, AA599070, AL079303, and U59628.
HSGAA12	899	971541	1 - 418	15 - 432		AA236764, and AA376628.
HRTAR64	900	575020	1 - 363	15 - 377		H45355, H49666, AA372974, N70354, AI909890, AA442334, R89350, AW062319, and N55639.
HRTAR31	901	698417	1 - 336	15 - 350		AA372947, N44034, and Z96074.
HRTAP73	902	560932	1 - 589	15 - 603		
HRTAN72	903	766328	1 - 247	15 - 261		AA372711, AA372710, AI524360, AA603323, AL037910, AW377756, AA508478, AA584125, AA878149, W42588, AA339692, AI953764, AL038533, AA228349, AI818770, AA094320, AA371620, AA664320, AI637960, AA321392, AA829154, AA828739, N84446, N94011, AW076090, AF109907, AI050331, AC006559, AC005844, AL035467, AF049895, AL050348, AL031289, AL023799, AC004525, AC000052, AL117258, Z95114, U73169, AC006064, AC005690, AC004612, AF069291, AC005189, AC004702, AB020866, AL121694, AC006449, AC007077, AC005632, AL096712, AC004558, AC004983, U91326, AF001550, AF134726, AB023050, AP000547, AC005726, AC005293, Z97184, AC006167, AP000502, AC004812, Z98949, AC005669, AP000511, AC005479, AL049589, AC002544, AD000092, AC006251, AC003101, AC007687, AP000235, AP000148, AC004783, AL049694, AC004590, AL133245, AC004813, AC009514, AJ133269, AC005209, AL031274, AL021578, U95742,

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HRTAN70	904	524889	1 - 263	15 - 277			AA372707.
HRTAN65	905	753913	1 - 467	15 - 481			W02953, AA372702, AA059274, Z44368, and AA527005.
HRTAN23	906	675124	1 - 273	15 - 287			AA372600, H57420, and Z69922.
HRTAE57	907	871385	1 - 479	15 - 493			T84441, T87483, H10262, T87081, AA227870, AI142241, AI142239, AI142363, R34809, W31798, AA056667, AA131958, Z44312, W19601, N73145, W95957, W95790, AA076461, AA372457, T30672, AA172239, AI207438, T34511, N45246, W23814, Z44333, AA044187, AA151085, AW362870, AF201947, and AF082526.
HRTAD37	908	708782	1 - 410	15 - 424			AI033098, N51040, AA248728, and AA372391.
HROEA53	909	838825	1 - 625	15 - 639			H16090.
HROEA06	910	934673	1 - 784	15 - 798			H16700, R36273, AA001525, R35323, and AA021271.
HRODY95	911	838830	1 - 420	15 - 434			R28414, AB018308, and AL109827.
HRODX43	912	949765	1 - 344	15 - 358			N53877, AA922057, AI554027, AA761896, AA765458, AA812026, AA422154, and Z73359.
HRODU82	913	779482	1 - 895	15 - 909			N39010, AA703251, AA610001, N49555, N52454, N48204, N70226, W01015, AA909680, R95730, N76638, N59801, AA620768, N72668, T60944, T72454, AI247967, W04253, N77417, N54558, R92250, R95729, N70306, H54267, H77986, H66295, R98125, T74769, H59752, H70786, H70192, H82996, H70787, N59393, T71408, N33572, H71414, H48399, R83198, H90106, N77081, T98185, R83197, T97622, H83075, H60121, H90016, N49312, H91229, H82855, R96821, R91926, T97574, H91175, H77987, H60122, H67721, H59753, N54243, T61011, R98821, H71415, N78259, H83229, H54268, AJ242928, and AB017551.
HRODE08	914	958532	1 - 604	15 - 618			AW368057, AI692660, AA715719, and AI808462.
HRODD02	915	918978	1 - 426	15 - 440			R98174.
HR OCC67	916	751223	1 - 705	15 - 719			AI127460, AW419346, R80085, R53734, AI475201, AI373960, AA225023, AA169396, AI973283, and AI035400.
HR OCC38	917	709348	1 - 279	15 - 293			H67640.
HR OCB26	918	812019	1 - 439	15 - 453			AA039396, AI096343, AB022430, AF035448, and AF035408.

HROCA33	919	701847	1 - 427	15 - 441	H84680.
HROBZ37	920	708773	1 - 666	15 - 680	R99605, R99710, R99682, R99576, and AC002073.
HROBY02	921	918972	1 - 499	15 - 513	AI871120, and AI391487.
HROBW35	922	707622	1 - 660	15 - 674	T83735.
HROBU31	923	693831	1 - 591	15 - 605	N38913, and AA565798.
HROBU02	924	951649	1 - 385	15 - 399	R07729, AA228880, H60779, H49171, H95212, H68371, AA203416, AW009618, AA296635, AA490628, and H61001.
HROBR02	925	918985	1 - 508	15 - 522	AW451235, AI694586, H30117, AW451997, AW452091, and Z58991.
HROBL46	926	718638	1 - 458	15 - 472	T90904.
HROBH25	927	677574	1 - 560	15 - 574	H39085, and AC006443.
HROBG67	928	751230	1 - 374	15 - 388	R09792.
HROBF19	929	668013	1 - 447	15 - 461	N29851.
HROBD79	930	774558	1 - 643	15 - 657	N69648, N72687, and H70701.
HROAZ07	931	973603	1 - 502	15 - 516	
HROAW79	932	774604	1 - 447	15 - 461	R22240.
HROAV11	933	966329	1 - 321	15 - 335	T86201, and T80955.
HROAU03	934	923381	1 - 327	15 - 341	AA455823.
HROAS95	935	795621	1 - 627	15 - 641	AA053433.
HROAS28	936	685982	1 - 368	15 - 382	T86999, T99364, AI536908, AA470779, N32944, AA113170, AA911448, AW301491, AI865309, AC004765, AL049278, and Z85986.
HROAQ54	937	729168	1 - 396	15 - 410	T98456.
HROAL96	938	867080	1 - 673	15 - 687	AI887748, AW168158, W45355, AW303882, AI805418, AW438620, R62625, AI859373, AI686763, AA724880, AA694428, AA994785, AI569360, H64285, AI689362, AI354846, AW167889, H38775, AA226178, AW189456, AA917499, AI538416, AI376429, AI459109, AA659415, AI364174, W15507, AI435013, W74197, AA284943, AA479784, AA844193, AI589336, AI539530, AW195028, W60989, R53803, AI262183, AA586992, AW130476, AA506665, AI631868, AA468260, R53814, R62615, AA226522, AI280811, H80229, T10601, W79840, AW378719, AW051240, AI915756, R30965, AA128014, AA128057, AL037910, AI918612, T81774,

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HROAJ83	939	781394	1 - 466	15 - 480	R92032, H57725, AI200922, and AI200919.
HROAI61	940	742084	1 - 596	15 - 610	AI769476, W77827, AW269989, AI339358, AI215593, AA973129, W72191, AW450132, N95340, AA247151, and W24962.
HROAG39	941	526488	1 - 186	15 - 200	AC005484, and AC004962.
HROAF96	942	830769	1 - 446	15 - 460	H05826, AI214244, AI088894, AI079203, AW055078, AA400706, Z40251, AA127228, W35112, H20787, H77308, AA004682, AA505056, W23679, AI23257, AI359089, AI863034, AI125459, AA991291, AA853910, AI253662, D20136, AA513204, AA507670, AI077992, W38818, and AF092132.
HROAE84	943	881995	1 - 772	15 - 786	
HROAD39	944	597055	1 - 425	15 - 439	R25632, and AC005375.
HROAD06	945	954694	1 - 431	15 - 445	R84228, and R96571.
HPASF63	946	745524	1 - 434	15 - 448	H52977.
HPASE19	947	672016	1 - 304	15 - 318	H10603.
HOCNF65	948	859585	1 - 521	15 - 535	H23470, AL041560, AI380171, AW297334, AW206916, AI421917, AA621171, AW296685, H47027, AI140475,

					AI361272, AI652621, AW207643, Z38296, H46488, AL041559, HI7831, and F01565.
HNSMD08	949	958337	1 - 709	15 - 723	N28216.
HNSMC05	950	840216	1 - 646	15 - 660	AA084461, AI042069, and AL110249.
HNSAA51	951	971484	1 - 732	15 - 746	AA976830, AI934102, AL119457, AL119324, AL042544, AL119399, Z99396, AL134524, AL119443, AW392670, AL036418, AL038837, AL037051, AL036725, AW372827, AL036858, AA631969, AW384394, AL119418, AL119484, AL039074, AL119319, AW363220, AL119522, AL119497, AL134902, AL119391, U46351, AL119464, U46350, AL036924, AL119355, AL119483, AL119363, AL037205, U46341, U46349, AL119341, AL038509, AL039564, AL119401, AL039085, AL119335, AL119396, AL039156, AL039108, AL039109, AL039128, AL119439, U46347, AL119496, AL037639, AL119444, AL134525, AL037094, AI142139, AL039659, AL043019, AI142137, AL037526, AL037085, AL037077, U46346, AL038531, AL037526, AL036190, AL134536, AI142131, AL036268, AL134526, AL042614, AL036767, AL037082, AL042984, AL042965, AL042975, AI142132, AL134538, AL039625, AL039648, U46345, AL038851, AL045337, AL036238, AL038520, AL039851, AL042551, AL042542, AL038447, AL039678, AL039629, AL042450, AL043029, AL039386, AL037615, AL043003, AB025008, AB025009, AR060234, AR066494, A81671, AR069079, AR023813, AR064707, AR043113, AB026436, and AR054110.
HNKCM03	952	922136	1 - 439	15 - 453	AI263076, AW272255, AI792912, and AI734009.
HNKAZ51	953	947067	1 - 820	15 - 834	Z99396, AL038837, AL037051, AL036725, AA631969, AL039074, AL036418, AL039085, AL036858, AL039564, AL039156, AL038509, AL039108, AL039109, AL039128, AL036924, AW392670, AL037094, AL039440, AL039659, AL038531, AL036196, AW372827, U46341, AL119497, AL039625, AL039648, AL045337, AL038447, AL036767, AW384394, AL037082, AL037526, AL036190, AL037639, AL039678, AW363220, AL039629, AL119457, AL119319, AL039423, AL036238, AL119363, AL039150, AL119391,



HNKAO08	954	955691	1 - 976	15 - 990	AL038520, AL040992, AL042909, AL119335, AL119443, AL037077, AL119496, U46350, AL119324, AL119484, AL119483, AL037726, AL119341, AL119355, U46346, AL119522, AL038851, U46349, AL039410, AL119396, U46351, AL036998, AL037615, AL037085, AL036733, AL039386, AL134528, AL036268, U46347, AL119418, AL119444, AL042614, AL042975, AL119439, AL037027, AL037178, AL134533, AL045353, AL037205, U46345, AL134518, AL134524, AL036765, AL036679, AL042965, AL119399, AL036973, AL036191, AL042984, AL042970, AL134531, AL142132, AL042551, AL134538, AL134542, AL042450, AL036719, AL119488, AL042544, AL043019, AL043029, AL037021, AL042542, AL043003, AL037054, AL036836, AL036158, AL119464, AL036774, AL036886, AL036999, AL036964, AR060234, AR066494, AR023813, A81671, AR064707, AR069079, AR054110, AB026436, and AR064706.
					AI979261, AI423298, AI640707, AW341832, AI032611, AI818044, AI299508, AI911386, AI270418, N71836, N59447, AA826491, R54110, Z25159, Z39436, AA587421, T32982, F09044, AA769767, and AL031003.
HNKAB83	955	914959	1 - 548	15 - 562	AI566101, AA721082, H87850, AI949699, AI160614, AA417266, AW439812, AI093245, AA928184, AI695423, N29576, AI761215, AI720751, AI138449, AA514412, AA580190, AA825290, AI267574, AI701478, AI686337, Z39053, AI498485, AW193765, AA032214, AI186466, AW138685, AI026619, AI301500, AA876544, AW073960, D62736, AA602996, and AI422653.
					AI085377, AI743872, AW170449, AI769100, AI080610, AI148232, AI472832, and AI086668.
HNJDR12	956	968978	1 - 505	15 - 519	AI128489, and AA058692.
HNJCE58	957	927451	1 - 918	15 - 932	T77126.
HNJBY05	958	928680	1 - 439	15 - 453	
HNALB40	959	507439	1 - 492	15 - 506	T61125, AI357584, AI357594, AI370909, AI653509, AA740653, AI262181, AA932188, AW338203, AA287566, AW004871, AI932958, AA287565, AA939295, AA907858, C04769, AA759017, AA707452, C05477, F31371, and AI814938.

HNALB10	960	968198	1 - 258	15 - 272	AA443771, AI298995, AC006328, and AC005630.
HNAAE09	961	888913	1 - 493	15 - 507	Z99396, AW392670, AW384394, AW363220, AL119497, AW372827, AL036418, AL119443, AL038837, U46347, AL037051, AL036725, AA631969, AL119396, AL119391, AL119341, AL119319, AL119457, AL119324, U46341, AL119483, AL119484, AL119363, AL119355, AL119335, U46350, U46349, AL036858, AL119522, AL119496, U46351, AL039074, AL036924, AL042975, AL119399, AL119418, AL134902, U46346, AL119444, AL134533, AL134529, AL134527, AL042614, AL037205, AL119439, AL038509, AL039564, AL037085, AL043003, AL042965, U46345, AL134920, AL134528, AL037094, AL037526, AL042984, AL036196, AL119488, AL042551, AL036190, AL134536, AL134538, AL042433, AL037639, AL042970, AL038520, AL039659, AL042450, AL142134, AL036767, AL037082, AL036268, AL042542, AL042544, AL043019, AL043029, AL037077, AL036238, AL036998, AL036733, AL042909, AL038447, AL037027, AL119464, AL036774, AL037178, AL038851, AL037615, AL037021, AL036765, AL036719, AL036191, AL036679, AL039410, AL036886, AL031058, A81671, AR060234, AR066494, AR023813, AR069079, AR064707, AR054110, and AB026436.
HMZME85	962	861084	1 - 791	15 - 805	AA582005, N31378, AL133058, AL137583, AF115389, AF089744, AF099082, AF131098, AF131100, AF198106, AF131097, AF198105, AF131099, AF131101, AF198104, AF131096, AF114753, and AF131102.
HMZME57	963	734417	1 - 304	15 - 318	T54435, and T54434.
HMZMD49	964	722624	1 - 429	15 - 443	AA046400, AI769960, H87413, AI458141, and AI743200.
HMZAE53	965	868116	1 - 304	15 - 318	AA167323, AA167320, AI821552, AI821518, AA167144, and AA167062.
HMZAC09	966	625188	1 - 748	15 - 762	AA446075, AA430264, AF127980, AF043977, and AB026833.
HMZAA34	967	703755	1 - 614	15 - 628	AL138057, R32100, H03041, AL046696, AI679639, and W23313.
HLXNC18	968	973906	1 - 666	15 - 680	
HLXNB04	969	926933	1 - 442	15 - 456	W01053, R83641, R98509, and AF120999.

HLQIF28	970	856619	1 - 372	15 - 386	T64673, T74667, T58830, AL121739, AB024079, AL021879, and AF104312.
HLQHD03	971	856624	1 - 460	15 - 474	AA402102, AA401945, AW193493, AA961197, AA384039, AA515435, AA640979, AW407919, T60699, F37223, AA737154, AL119123, AW371267, AA836811, AI648558, AI597832, AA557879, T47739, H85616, AA595669, AA354507, AW265654, AA548029, AA714595, AI580898, AI360514, AA515937, AA664604, AA747375, AA368329, AI633185, H86301, H86264, AA713715, AI038990, AI791189, AA468051, AI338509, AA831388, AI469624, AA805841, AA658937, AA467988, AA947370, AW243960, H58472, AF150152, AA010672, AI367721, AA326410, F31799, AA779783, AI928790, D58782, AA394271, AA632960, AA342901, AW408063, AI281909, C75026, AI832865, AI587389, AI471534, AA723287, H40410, AI587400, AI683577, AA663306, H72688, AI978792, AA703684, AI206785, AA525209, AW075979, AI110770, AA526193, AA646666, AA262752, AI004591, F23255, AA704643, AA654968, AI570943, AA121919, AW028429, AA368936, AA065087, AA493713, AA449523, AA350859, AW074398, C05999, F37052, AI801482, AA679872, AI377413, AA493632, T40612, AA811580, AA493642, AI284640, AA054106, AC007021, AF094481, Z69720, AC007092, AC007536, AC007114, AC009721, M87918, Z75895, AC002530, AC005940, AF200923, AF118569, AC006530, AC000094, AC000085, AC006397, M63543, X81637, M63544, AC007542, Z98949, U02044, L78810, Z96568, AC005933, AF091512, AL021997, AJ003147, AC005695, AL049780, AC002984, AL079299, AC006441, AL031592, AC005593, AF104670, AC005779, AC005757, AC002288, AL109984, U63721, U78045, AC004892, AL109956, AC004185, AC006468, AF045555, AC002287, AC005245, Z49235, AC004973, AC005018, AC004750, AC004647, AC003111, M87914, AL135744, AC004744, AP000509, AC006237, AL121655, U91319, AB001523, AC010197, Z97054, AL031584, AL031005, AC004159, AC002404, AC005777, Z98051, AC005901, AC004531,

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HLQGZ73	972	856638	1 - 592	15 - 606	AA142959, W95902, AL288628, AL367025, AA156599, AL633973, and H40855.
HLQGUI1	973	965781	1 - 1004	15 - 1018	AL739061, AA448989, AW170611, AW292930, AL472107,

HLQGP25	974	893692	1 - 511	15 - 525	AI804333, AI433329, R98898, AW243086, AW000993, AI380481, AI128676, AI078025, Z42061, AI271847, AA704936, N52275, R98672, AA449455, and Z38340.
HLQGP12	975	969516	1 - 904	15 - 918	AC004458, AI049759, AI035410, AC005319, AC005277, AI022320, AC005800, Z70281, AI008726, AI135744, AC002312, AC006475, and AC005529.
HLQGA01	976	915066	1 - 736	15 - 750	AI076198, AI248210, R08660, R08563, AA386291, AA386292, AA386290, W26527, and AC004913.
HLQFS05	977	928264	1 - 486	15 - 500	AI248815, AA778830, and R98466.
HLQFQ08	978	961154	1 - 485	15 - 499	N25064, and AI133216.
HLQFE53	979	856700	1 - 855	15 - 869	AA976655, AI586970, AW062875, AW207728, T58992, and AC007114.
HLQEW11	980	966019	1 - 445	15 - 459	AA399598, and AA054390.
HLQEN12	981	969694	1 - 634	15 - 648	W44531, AW080328, W44532, and AI378133.
HLQEN07	982	856733	1 - 296	15 - 310	AI624865, AI478349, and AC005336.
HLQEM06	983	934078	1 - 306	15 - 320	AA728974, and AC004621.
HLQED04	984	969543	1 - 548	15 - 562	AI610517.
HLQDV62	985	743401	1 - 334	15 - 348	AW295240, T58758, AW449145, AW024686, AA865601, AI671382, AW129211, AI310515, AI310517, AA582271, T72069, T68855, AA894912, AW294154, AA962431, AW275359, AA862395, R92627, AI245451, AI632011, C20969, AI934344, AI431736, AI493860, AI522042, and AC003034.
HLQDV01	986	916190	1 - 527	15 - 541	AI347695, AI884353, AI075047, AA496969, AI051946, AA406632, AI242449, AI248927, AA694032, AI432457, AI656905, H45274, AI802069, AA931335, AW241988, AI914978, AI808628, AI824824, AI808753, AW002992, AA912515, AA490567, and AF072934.
HLQDU64	987	746435	1 - 431	15 - 445	AA913936, N72783, and AC007281.
					R50022, T18597, R29657, D59751, R45895, AI557262, AI557864, Z32887, AA585098, D60844, D59436, AA585325, AI541356, D60765, R28735, R29445, AI526078, AI525500, AI525316, AI541365, R28892, AI541205, AI525556, AI557731, D61254, AI170832, AA585101, D54897, R29218, D57491, AA585439, AI546971, C15737, AA585476, AI557155, Z32822,

C15406, D53161, R28895, Z28355, C16315, AI557084, AA585155, C16293, AI546875, AA283326, R28965, R28967, AI557740, AI526140, C15069, D61185, D55233, AI541383, AI557734, D53472, AI546999, AI547250, AI547196, D53447, AI525306, AI557763, C16294, C15120, C16300, D52835, AI541374, AI541535, C14208, AI547039, AI526184, AI540974, C16292, AI540903, AI541346, AI557809, AI525431, AI541517, AI541013, AI557602, AI546945, AI557787, AI526016, Z33559, C15762, AI546829, AI557727, AI547137, AI541034, C16305, Z30131, AI525339, AI557408, AA585356, AI526194, AI557718, R29179, AI541523, AI557807, AI546921, AI541307, AI557808, AI526191, AI547202, AI535660, AI546996, AI540967, AI546891, AI541321, AI547006, AI535639, D60730, AI557533, AI557758, C16296, AI557264, AI536138, AI525320, R29177, D57186, C14391, R29262, AI525286, AI526109, C14322, AI525856, AI541527, AA585453, R29172, AI526113, C16290, AI557279, AI541027, AI556967, T19407, AI526195, AI557238, AI526024, AI526073, AI526180, AI526112, D51433, D59458, D54850, AI557039, AA585430, AI525656, T41289, AA514191, AI526158, AI557852, AA174170, AI557082, AI541345, AI525332, AI546831, AI541510, AI524904, AA585117, AI540920, AI541422, T41329, AJ239433, AI541415, AI526117, C14210, AI546828, AI541506, AI524890, AI557799, AI557041, AA585434, AI557317, AI547189, AI546901, AA585440, AI541515, AI557285, AI526187, AI541075, C14723, AI540882, AI541492, AI541514, AI524891, AI526205, AI546954, AI541017, D61060, AI541390, AI557786, AI525168, AI526146, AI541508, AI525653, AI525114, AI557810, AI557796, AI540944, AI525076, AI541423, AI547026, AI547071, AI557785, AA585420, AI557802, Z69374, Y09813, AR062871, A25909, AR038855, Z32836, AR054723, X81969, AJ244005, Y16359, AF082186, AR038762, D50010, D13509, AJ244004, A20702, AR062872, AR062873, A20700, D78345, X82786, A43189, A43188, AR017907, AJ244003, X55486, X76012, AC005913, A98420, A98423, A98432, A98436, A98417, A98427,					
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HLQDT89	988	786115	1 - 803	15 - 817		T96700, T96593, T79642, T79728, and AC011604.
HLQDR89	989	972425	1 - 329	15 - 343		
HLQDR47	990	720145	1 - 335	15 - 349		R79023.
HLQDR15	991	660003	1 - 563	15 - 577		W78833.
HLQDQ72	992	973258	1 - 393	15 - 407		
HLQDP33	993	702276	1 - 440	15 - 454		AA135279, AA417119, Z98200, AC004800, AC006379, AC005826, Z84487, and AC006449.
HLQDM72	994	761347	1 - 622	15 - 636		T98543, and AC002565.
HLQDM03	995	923862	1 - 189	15 - 203		AA027217, and AL122007.
HLQDJ01	996	916193	1 - 468	15 - 482		AA765420, AI734264, T07769, AA494263, AA828062, AA167792, AA610219, AI287320, AA631480, AA804706, AI205101, AA594072, AA298969, AA491797, AW162442, AA613188, AA480792, AA524829, AA581247, AI733856, AI475616, AA584378, AI056177, AA442176, AA608612, AA410788, AA610494, AA228778, AA640797, AA984114, AA136577, AW327624, AA985391, AI806102, AI086830, AW328172, AW080440, AA811208, AI366464, AI042373, AA608588, AW130093, AW402817, AA773162, AW025074, AI588910, AA665199, AA101113, AI886338, AI031427, Z97832, AP000553, AC005291, AI031729, AC005179, M63543, M63480, M63544, AP000036, AI031120, AC002463, AC005086, AC007687, AC004019, AC004520, AC004131, AC000364, AP000556, I44140, Z97181, AI031311, AC005539, AF047825, AC009363, AC006312, Z95114, AI021937, AC005095, AF086155, AI022238, AC005701, AC006116, AI133304, AI031594, Z82198, AC005261, AC005844, Z85986, Z86090, AC020663, AC004241, AC005971, AC006009, AC005212, AI022336, AC006211, AC007686, AC002483, AI139054, AF104455, AI009178, AP000689, AC005754, AC004491, AC005695, AC005907, AC005940, AI050333, AC006138, AC005803, AI096763, AC004686, AF196969, AC005702,

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HLQDI75	997	856759	1 - 326	15 - 340	AI784258, AI003123, AA558404, AA857622, HS9611, HS9651, AI240755, R01574, AA632757, AA595554, AI187080, R98409, AA984920, R70883, R70884, AA602574, AA553579, AI566236, AI749306, D51809, F33820, AA385775, AI051539, AA371003, AA371410, AA501807, AA737523, T07420, AI567391, R77715, D51877, AA468058, T92803, AI282629, AA847499, F23268, AA384911, AW237905, F31575, AW302078, N70222,



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HLQDF69	998	754302	1 - 407	15 - 421		AI741424, AW379392, AI203575, and AI522301.
HLQDF27	999	682896	1 - 224	15 - 238		
HLQDE32	1000	707639	1 - 742	15 - 756		R13823, T31214, AA101560, Z25135, R61709, R35616, AA333729, and R94706.
HLQDC02	1001	919611	1 - 507	15 - 521		AW444819, AI223138, AI809436, N94628, AI869757, W23828, C01878, and AA320959.
HLQDB69	1002	934462	1 - 494	15 - 508		H84572, AA921736, C14111, AA193066, AA279233, Z44100, and AL137527.
HLQCZ83	1003	781052	1 - 373	15 - 387		AA004424.
HLQCZ46	1004	871684	1 - 951	15 - 965		AI935557, N53561, AI435571, AW104342, AI628733, AI950465, H57932, AA701378, AA410255, W86579, N91619, AA705304, AI239546, R85396, T54915, AA928077, R59888, R40761, AI076347, N68729, AI056635, AI910761, AI492415, AW299867, H58023, R59629, AA406529, T95812, H19427, AA689340, F09287, W86712, Z40128, T55082, T95811, F01868, N72520, and AL109938.
HLQCY79	1005	774827	1 - 581	15 - 595		W02640, H66605, N74443, T86668, N74391, R91408, R92668, H66604, H47090, H78955, W03155, H47124, and AC004139.
HLQCS58	1006	735841	1 - 484	15 - 498		AI091581, AA458633, AA455537, and AL022395.
HLQCQ09	1007	625412	1 - 420	15 - 434		AW449242, AA193381, AI343478, AI074563, AI143834, H66591, R02833, and AL031428.
HLQCP89	1008	689673	1 - 749	15 - 763		W85886, AI311917, AW237344, T86920, R02060, and W85970.
HLQCO19	1009	668521	1 - 609	15 - 623		T89987, and T87169.
HLQCK45	1010	488499	1 - 860	15 - 874		AA186729, H78234, H78434, R97547, AA628115, and AA992226.
HLQCI96	1011	823602	1 - 446	15 - 460		H70404, W67241, AI807620, AW170393, AI148673, AI700503, AI951537, AI418406, AW027328, AI372906, AI978898, AI355972, AA804574, AA577153, AA683135, AI375779, AI421626, AA922646, R50491, AW083779, AI086894, R71660, R70331, R80971, H45696, H04767, H50348, AI149104,

HLQCH67	1012	751481	1 - 692	15 - 706	AA350063, AI000283, AI336304, H04863, AA454614, AA948638, H48164, AA158079, N30114, AA040055, AA100734, H14248, H41004, H03390, AA935502, AW085023, AI873952, AA953342, R71761, AA488228, AA350336, R71772, AA330664, AA350335, AA558800, T47929, H21988, AI185581, AI355331, AA350333, W42753, N92553, AA380748, R80075, AA349208, AA366768, AI498026, AA488175, R79976, AI362566, AI372422, AA974799, H04088, R48548, AW247533, H52808, AA364212, H19508, AA380728, AI611852, W67185, AA313213, R24504, AA890444, R35881, N42220, AW381755, AA350334, AA455790, AA317877, AA188900, AI910306, W42696, AC006165, AB023051, AP000512, AF117234, AF085357, AF089750, U60976, U60977, AF145044, and U90435.
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HLQBS59	1013	566772	1 - 1256	15 - 1270	
HLQBQ19	1014	671928	1 - 365	15 - 379	H67959.
HLQBF91	1015	790408	1 - 522	15 - 536	N50005.
HLQBD38	1016	948694	1 - 458	15 - 472	AI217956.
HLQAX31	1017	693626	1 - 661	15 - 675	N76167, N64759, and AC002452.
HLQAP90	1018	787240	1 - 276	15 - 290	T39322.
HLQAO31	1019	698385	1 - 529	15 - 543	AA007275, R94668, W85761, R11426, AA677068, AA007276, AI033796, R94669, and R19176.
HLQAN75	1020	880815	1 - 474	15 - 488	R96337, H93374, H52073, AI278166, H83689, R44303, H52072, AI290552, R96336, and AF193806.
HLPBA84	1021	912828	1 - 536	15 - 550	AI057011, AA634414, AW062302, AA368329, AA507990, AW029626, AI114755, AI888050, AA351868, AA454041, AA773560, AL047480, AA015948, AI799421, AI337612, AA315052, AW439724, AA368659, F34151, H87756, AI620666, AA101744, F31575, AI298079, AA984829, H15241, AL034424, AC006317, Z82176, AL121603, AL132992, Z82195, AL096701, AL122020, AL121595, AC006312, AL022165, AL080243, AC006992, Z99716, AC007285, AC002554, AC005620, AC007546, AL080316, AL021707, AC008012, AL031655, AC004859, AL035458, AL031848, AC005972, AC005399,

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HLICU57	1022	871716	1 - 780	15 - 794	AA203741.
HLICS57	1023	734450	1 - 282	15 - 296	AA027810.
HLICR28	1024	686132	1 - 377	15 - 391	W86711, and AA248953.
HLICP76	1025	825536	1 - 781	15 - 795	H14920, N99605, H43830, AW241813, AA992585, H44756, AI800469, N62965, AI375065, N92659, H14627, AA897465, AA984538, Z40651, AL133626, and AC010168.
HLICO07	1026	952625	1 - 517	15 - 531	AL133721, AW052162, AI492031, AI640760, AA148591, AW242947, AW294183, and AA148722.
HLICL82	1027	779576	1 - 492	15 - 506	W04468.
HLICJ60	1028	739746	1 - 442	15 - 456	AA700817, T89766, AL248274, W90390, AA846955, W88458, T89405, AI023455, and AI023461.
HLIBZ10	1029	963973	1 - 325	15 - 339	R91346.
HLIBK17	1030	662438	1 - 478	15 - 492	R15403.
HLIBB54	1031	782180	1 - 283	15 - 297	N93782, AA430461, AA190961, and AA134507.
HLIDRT92	1032	791215	1 - 482	15 - 496	AA432137, T90468, and R02051.
HLDRP58	1033	735731	1 - 620	15 - 634	AA064968, and T82701.

HLDQV07	1034	952691	1 - 439	15 - 453	RI3965, and Z42716.
HLDQN90	1035	857062	1 - 149	15 - 163	AA441872, and AL022323.
HLDQH68	1036	835571	1 - 578	15 - 592	AA179351, and AC002352.
HLDQD92	1037	552019	1 - 658	15 - 672	H75477, H79155, AC004872, AC004562, and AC005144.
HLDQC57	1038	734475	1 - 797	15 - 811	AA429570, and AA429701.
HLDPE31	1039	697969	1 - 464	15 - 478	AA034053, AI085454, T91887, AI468274, and H78608.
HLDQX46	1040	719023	1 - 470	15 - 484	R87345, AA081495, H43858, and AF038458.
HLDOT85	1041	784331	1 - 818	15 - 832	RI8596.
HLDOS76	1042	770016	1 - 448	15 - 462	T69062, AA706202, AA984829, AA557945, F31811, AA371410, AI636734, D51877, AW089950, AA687542, AA663074, AA385775, AI439676, AI678476, AL039309, W63553, AA244181, AA714073, AI591134, AW079667, AW392414, AI368732, AW302670, AL042630, AA135988, AI343669, AI049504, AI309121, AA559890, AA595504, AA577141, D51809, AI207476, AI885465, AA302971, AW019964, AA523833, AA077619, AL039930, AI627168, AW272640, AW190277, AW193337, AF047825, AL049872, AP000501, AC007057, AC005899, AL049869, AC007201, AC002477, I34294, AC006581, AC002128, M87889, AC005231, AC004242, AF031078, AC005412, AF030876, AL121652, AP000557, AC005736, AL020995, AL049795, AP000065, AC004967, AC007308, AC002470, AC004257, AL135744, AL022313, AC000090, AL022721, AD000092, AC005919, AP000210, AP000132, Z97630, E15649, AC006450, AL022326, AC002546, AL117330, AL021453, AC007225, AC004938, AP001053, AL096766, AC003685, AC000075, AL031846, AL022323, AC007182, Z94801, AC003109, AC005486, E15653, AL022165, AC005667, Z81357, AL020989, AL031257, AL049748, AP000295, AC006088, U95739, AL133244, AL050333, AC004217, AC007227, AC006449, AD000813, AC002543, AC005694, AL022316, AC004185, U51561, AL049713, AF039904, AC018633, AL008730, AC005880, AC005670, AL139054, AP000497, AC005409, AF064861, AC002350, AL050318, AC006537, AC005261, AC004893, AC005046, Z83844, AC005884, AL109758, AC004150, AC007376,

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HLDOM43	1043	715254	1 - 536	15 - 550	H57686, AW328038, AW328039, AI681235, H67403, AL039390, AI249936, AI890907, AL042551, AL045166, AL046681, AI273179, AW152182, AL046137, AI633125, AI431315, AI915291, AI538564, AI884318, AI701097, AI499570, AI333104, AI364167, AI358271, AI888022, AI637584, AI499463, AI866484, AI302590, AI401697, AI638644, AI653979, AI687944, AA806719, AI702073, AI932620, AI580190, AI473536, AI818240, AI670002, AI433157, AI247293, T69241, AI499478, AW190194, AI689247, AW081133, AW167228, AW004606, AI432644, AI474646, AI694157, AI623302, AI635016, AW075667, AI654276, R40363, AI431307, AW167021, AI431316, AI698391, AI474699,

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HLDOK25	1044	678063	1 - 528	15 - 542	C75377, AA527038, H93171, AA862312, AA846923, AI636734, AI368862, AA302978, AA809186, AW023111, AA297443, AA599080, AA568127, AA632765, AA938390, AW007424, AI138199, AI340858, AI824541, AW192402, AA548610, AI356440, AI583936, AI118925, AI471467, AI362442, AA629888, AI751753, AA630122, AA808982, AA502207.



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HLD0E06	1045	922162	1 - 524	15 - 538		AA866169, AA446868, AA505738, AI055812, AI887206, AI923981, AW084907, AA485906, AA037428, AA443821, AI680166, AW361703, AI439919, AI689153, AA622493, AI476741, AW361713, AI365655, AA586973, AA772452, AA923558, AI565628, AI304714, AI244508, AA099053, AA554338, AA857533, AI300683, AW293561, AW149707, AI186551, D25678, T69023, AI682452, AI265996, AA037532, H49206, AW361850, AA902603, AI538000, AA142864, AA725579, D52941, AI630692, AW026668, F32568, AW293557, AI073910, AA136784, C15445, W15588, AA028909, AI370704, T82843, AW361878, AA043415, T30817, AA845713, AA594615, AW340363, AW242261, AA877034, AI309555, AW075588, AI828409, AA558035, AW148338, AI285135, H03187, AA534866, R27376, AA331136, AA847452, T31464, AA136668, R31732, T36021, AA370723, W24128, AI024538, AA953603, D80641, D61001, R81710, AA452178, AW118866, AA098897, AA876501, AW274233, AI932889, T60260, AI140225, AI041191, AI806267, AA425294, R27377, AA693413, AA446982, AA507290, AI932451, R24642, AA424069, AI133679, R56822, AI914460, AI826456, W31664, AA360213, AA486511, T61641, AW129345, AA506474, and AA946889.
HLD0D83	1046	724046	1 - 648	15 - 662		AA781412, AA719282, AA706936, NS8009, AI095639, AI636021, AI188542, N64210, AA781918, AA706954, H48268, AI695180, AI198594, AI474680, AI244280, N54516, T67631, AI927296, W00987, H48358, AW194801, N57934, AA970232, AW102737, N74650, AA843702, N76219, AW024654, T67512, N76440, AA885957, AW001061, T70355, AF169017, U91541, AP001101, L16507, and AL109817.
HLD0C67	1047	689240	1 - 442	15 - 456		H68576, AA232811, AA256904, AA046229, AA135267, AA359782, H46783, H41887, AI922726, AA027883, AW248488,

HLDNR75	1048	767294	1 - 356	15 - 370	and AI972277. H58931.
HLDNR54	1049	729853	1 - 343	15 - 357	AI948492, and AC002401.
HLDNL92	1050	792694	1 - 387	15 - 401	R06001.
HLDNL57	1051	963552	1 - 657	15 - 671	AA043317, AA058606, AI872402, AA527086, AA532449, AI524324, AA514662, AA043318, AA659799, AI636322, AA470758, AA971274, T61144, T52957, AI865691, AA861977, AI022054, AI209021, AA602448, AA640580, and AI055999.
HLDY07	1052	952751	1 - 682	15 - 696	H93481, and AL033397.
HLDSD06	1053	934929	1 - 541	15 - 555	AI206213, AI918833, and Z94865.
HLDWCW15	1054	705466	1 - 577	15 - 591	R89288, H72622, H47983, and R00532.
HLDLCU74	1055	765307	1 - 227	15 - 241	AI682666, AW139277, AI338770, AI761828, R50463, and Z69719.
HLDCE01	1056	916444	1 - 295	15 - 309	AA994155, AA628622, and AL049742.
HLDBW64	1057	746545	1 - 495	15 - 509	H49820, AI015194, AA885084, AW294420, AL045755, and AL046210.
HLDBV65	1058	764915	1 - 448	15 - 462	W61047, AI905432, AI905450, AA147405, AA469989, AW176008, AI816821, AA425819, AI905502, AA309139, H19938, AA443501, AW301071, AA460750, AW003882, AA029238, AW369505, AA040824, AW003283, AW393141, AF059617, U85755, and M96163.
HLDBT71	1059	760347	1 - 684	15 - 698	N52837, AA488637, AI885757, AA005131, AI241473, AW292454, AA705676, H57758, AA134965, AA135046, H56907, AA486018, AF144233, and AL031666.
HLDBN55	1060	731734	1 - 585	15 - 599	AW250883, AI538703, AA133554, AA635020, AW246754, AW246544, AI693985, AI830799, AI371038, AI302734, AA515421, AA594483, AI761866, AI703350, AI336388, AI817132, AA932660, AA469087, AI809399, AI702168, AA987492, AI682236, AA953756, AA514434, AI342818, AF176110, AF147787, AB028021, Z57610, Z60048, L10409, U04197, X74937, L09647, Z57611, and Z57609.
HLDBN38	1061	678424	1 - 772	15 - 786	R37780, Z40536, F02088, AC007567, and AF172277.
HLDBN03	1062	924100	1 - 843	15 - 857	AI278279, R56805, T99445, R54310, R13679, and R35831.
HLDBI09	1063	625542	1 - 463	15 - 477	W86312.

HLDBE09	1064	625554	1 - 449	15 - 463	AI679782, AI963770, AI046409, AI284640, AA490183, AI270117, AW193265, AI334443, AI345654, AI613280, AI281881, AI064864, AW303196, AA720702, AW274349, AI042853, AW301350, AW249224, AI119691, AW419262, AA521399, AA610491, AA521323, AI138455, AI589230, AI801482, AI570261, AA828704, AA551503, AA877817, AI048626, F36273, AW021583, AA491284, AI567076, AA468022, AW265393, AI623720, AI421841, AI499938, AI044858, AI754658, AW072923, AW406755, AI041690, AA679514, AI044940, AI350211, AA522942, AA503015, AI431303, AI457397, AA491814, AI499503, AI696962, AI345681, AI345675, AW265385, AW407578, AI355206, AW073470, AW020340, AW238278, AI254615, AI133164, AI358229, AA526787, AI270559, AI164251, AW265170, AA584201, AA569471, NS3150, AA581903, AW088202, AI039958, AW270382, AW270270, AI038705, AW029038, AI890918, AI251436, AI357901, AA587604, AI610920, AW304584, AA682912, N48230, AI805607, AW162049, AW438643, AW327868, AA219129, AI929531, AW062724, AI732865, AI339850, AA587256, AI625244, AI473943, AI919265, AI962050, AI110770, AA523815, AW340844, AI038785, AA491831, AI038474, AA493471, AA483223, AI537506, AI368745, AI119984, AI918421, AW028429, AI053672, AI890348, C06327, AI046205, AI799642, AI888518, C05755, AI307201, AW301809, AI042420, AI365988, AA623002, AA507824, AA244357, AA523821, AI619997, AW408717, AA908687, AI368256, AI246119, AA577906, AA493708, AI129446, H71429, AI046457, AW020992, AA665330, AI567674, AI610159, AA806796, AW238583, AI801600, AI043009, AW274346, AA470969, R24887, AI951863, AA630362, AI860020, AW376931, AI305547, AI249997, AI345518, AI289067, AI379719, AI061334, AW163293, AI633025, AI471481, AA598425, AI375710, AA713815, AA515829, AI344844, AA683258, AW166815, AI278997, AA582911, AI434706, AI732786, AW193432,
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AL121235, AA584145, AI688846, AI471572, AA765170, AI653636, AW261871, AW080134, AW083402, AL138265, AI890923, AI469968, AW104748, AL043719, AA594725, AA780515, AI340453, AI679132, AI341664, AA613203, AI654247, AA653618, AW302013, AI538852, AW276827, AA101689, AW169151, AA613227, AI049722, AI561060, AA469451, AA723017, AL042753, AW088616, AI251002, AL120687, W79504, AA837084, AI890928, AA553666, AA599920, AA525190, AI358571, AA610493, AA559290, AA523837, AI357288, AC005280, AC005484, AC004263, AL031005, AL031123, U62317, AC005755, AC002549, AF109907, AC004087, AB023049, AL109753, AC004858, AL035415, AL117352, AL096774, AL096791, AC006285, AC005234, Z83840, AC006430, AP000114, AP000046, AC007637, AC006205, AC003007, AP001172, AE000658, AC003006, AC005940, AL035658, AJ010770, AL133448, AL031729, AC005771, AP000348, AP001054, AC005288, AC005072, AJ003147, AL021368, AC009516, AC005632, AC016831, AL109758, AL031651, AP000555, AL121653, AP000553, AC008079, AL031681, AC005837, U95740, AP000557, AL023807, U80017, AC007358, AL022237, AC004941, AC007263, Z99758, AC005011, AC007308, U85195, U07000, AC004862, AL022721, AC002470, AC004675, AC007227, AC005257, AF042090, AC003101, Z98257, AC008372, AL050341, AC006449, Z99716, AC003684, AC007450, U91321, AC005785, AF196971, AL139054, AL008725, AL031276, AC009405, AP000117, AL023284, AF088219, AL035587, AC006001, AL096776, AC018633, AL031121, AC005622, Z93241, AL050318, AC005488, AP000359, AC007216, AC004491, U62293, AC005971, AP000689, AC005520, AC006998, AC007488, AL121652, AC006137, AL050347, AL034420, AL109798, AC005074, AC002525, AC006960, AL021977, AC006019, AL022323, AC002429, AC002350, AL049869, AC006011, AC005089, AC006040, AC003074, AC005295, AC005324, AC006213,				
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HLD09	1065	625551	1 - 454	15 - 468	AC005390.
HLD02	1066	920039	1 - 429	15 - 443	AI610448, N50597, AI708290, AI769304, W38693, AA236802, W20094, AI871973, AA299214, R87631, AI935619, AI050159, AC007546, AL022316, AC005829, AC005736, AC005800, AC005049, AC007151, AC004195, AL023575, AL109984, Z99128, and AC005921.
HLD10	1067	964582	1 - 453	15 - 467	D59341, and AF000962.
HLD21	1068	713680	1 - 451	15 - 465	AI608719, AI081552, AI278617, AI609398, AA621655, AA421224, AI290739, AA421214, AA868455, AW193527, AA868840, AW009516, AW001133, AI689150, AA610770, AI376946, AI735188, AI567964, AI284299, AI022091, AA993670, AA911941, AA888156, AI754809, AI273254,

HLDDB08 HLDAY58 HLDAY38	1069	959385	1 - 188	15 - 202	AA873585, AI743002, AW009876, AA602889, N40529, AA947889, R69521, AI277633, AA488241, AA460139, AA425965, AA579086, AI241348, AI300301, AA612762, AA421945, AA843194, T70058, AI190110, AA449898, AA581663, AI026923, AI090471, AA550844, AI471315, AA622170, AW250846, AA410582, AI301856, AA402945, AI350362, AA468762, AI080736, AA443534, AI268605, AW245161, AW406807, AA078825, AA449842, AA989498, AA662376, AA857872, AW402201, AA683333, AW403534, AA993166, AA429053, AA847314, AI753847, AA468742, AA468553, AA421946, W94599, AA602504, AA830904, AI018058, AA830858, N90006, AI880407, N63003, H23088, AA076631, AA155589, AA216765, W95828, AI269128, AA429082, AA476292, F36072, AA864547, AA086637, AA351368, AA258525, T34731, AA693504, AI872357, R87220, AA857088, AI160438, AA587426, N79911, AA364554, H14233, H30244, AA099847, AA837812, AA455853, AI364726, F37916, AA654151, H87247, AA335313, R87285, AA405877, R84553, AA349834, H30633, F00281, N31446, F09159, AI879829, T36108, AA758410, AI688327, H96271, W00489, H87295, Z28833, T74871, AW014579, AA405186, AI005580, AA844795, R87446, F34288, W05255, AW152260, W19804, AW250093, M62217, R45183, R20760, AA665325, AA078793, F36790, AA887570, AA365385, AA243274, AA429249, AI343791, F32088, Z41560, AW247954, AI244591, AA778048, AA988319, AA773338, AA991819, AA379651, AA460736, D54442, F02045, AA382483, AA365451, AA280940, AI474244, N98909, AI037768, AA642283, N53896, AA316956, AI524279, AA085173, AI581582, AA974346, AA911791, AI973107, AA983218, AI417506, H49168, R85162, AA384134, D20373, AW059596, AA055276, L38995, S75463, X84694, L38996, and Y11796.
	1070	736027	1 - 468	15 - 482	
	1071	709140	1 - 453	15 - 467	
					C04863, N53185, N54200, and N54238.
					T39217, F07212, AI299882, AI309979, AA804297, AA729512,

AI918419, AA809635, AA650447, AA620510, AL037714, AW162750, AL118925, AA570441, AA715955, AL046830, AA525293, AA508036, AW102811, AA582746, AA654482, AA370742, T85570, AW263867, AA158549, N22506, AI192440, AA937809, R70883, AA074351, AA581247, AA133332, W72660, AA719523, D51809, AA627276, AA516214, AA502207, AI298079, AA938390, AI492776, H85808, AI273148, C14480, AL041013, AA515728, AA678845, AW162227, AA551268, AA312559, AI732635, AI732128, AL040430, AA728938, AA612578, AW265342, T48856, AA452887, AA911582, H68110, T11709, AI929796, AI799421, AA713724, AA282951, C17794, AI85889, AA806804, AA071045, AW022891, AA629866, R70884, AA346436, AI969639, AI753536, R93642, AI433503, AI446561, AL134167, AA634926, AI912401, AI198718, H09267, AI819391, AI049955, N23241, AA381150, AA320105, F26713, AA528496, AA092704, AA586433, AW407889, AA554257, H79586, AI866377, AA385775, AA091982, R83068, AI669421, AA315361, AA229422, H73306, AA936718, AI915081, H43183, AI479068, AA297490, AW023111, R93235, AW440451, AA632556, AI800426, AA715968, W96522, H67064, AI683514, AW340912, AA635413, AI274011, AA588611, AL079734, AW247389, H58354, AA225890, F31575, AA226085, AI800345, F33505, AA486877, H69966, AA084609, R96175, AI282629, AA757753, AI671077, H64715, W01359, H87756, AI580906, AA993138, R42733, H59878, AW166920, AA188940, AI963029, AA594591, AI609972, T55459, H63660, H59886, AA878407, AI302156, AW192373, AA303059, AA644090, AA581404, AW166925, AA527877, AI885060, AW272599, R96427, AI963679, F26801, AI056046, AL119247, AI003503, AA737114, AA809153, AA728880, AA558404, N64439, AL041895, AA595554, AA837771, H66519, AL048002, AA296603, AA640825, AA302690, AA610255, AI914713, AA332013, AA528566, AA583245, AA603264, AI810584, AA445908, H71659, AA371410, AA838091, AI589403, AI051488, AI821805, AA714524, N92813, AA653955, AI306717, AI821056, R08161,					
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HLDV13	1072	657191	1 - 458	15 - 472	
HLDV01	1073	916462	1 - 466	15 - 480	
HLDA12	1074	970634	1 - 450	15 - 464	R38926, and AF131782.
HLDAK33	1075	857107	1 - 441	15 - 455	H55379, AB002328, AF072441, AP000352, and AF061947.
HLDAJ38	1076	709138	1 - 464	15 - 478	R00600, AA618364, and AL049557.
HLDA31	1077	586638	1 - 289	15 - 303	AC005753.
HKCTA23	1078	877228	1 - 486	15 - 500	R80472, and R64402.
HISET33	1079	974559	1 - 500	15 - 514	
HISEQ03	1080	923095	1 - 527	15 - 541	R95137, U61375, and U63312.
HISEI01	1081	915375	1 - 402	15 - 416	AW163174, H79412, and W77826.
HISEF78	1082	841308	1 - 796	15 - 810	AA160180, N92184, R62724, W49839, AA370734, AI478927, AA451825, AW082565, AW172889, AI670112, H43466, H71118, AA628416, AW071645, AI566751, AA160181, AI655849, AI637656, AA833797, W39691, AI342003, AW339069, AW136578, AW090555, AI686125, AA860942, AA372829, AW136580, AA449129, AI970182, AA454157, AW136585, AI138477, AA846238, AI049996, and AC005071.
HISDW49	1083	928682	1 - 979	15 - 993	AI687430, AI889377, AI693929, AI870875, AI942476,

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HISDQ54	1084	843345	1 - 652	15 - 666	AA085696, Z21102, AA780407, AA463908, and AB020633.
HISDL84	1085	782286	1 - 314	15 - 328	R52393, and AA723927.
HISDF08	1086	958417	1 - 585	15 - 599	AA588648, AA127281, and AL049713.
HISCO82	1087	975205	1 - 697	15 - 711	AC005295, and AC004854.
HISCO10	1088	964285	1 - 602	15 - 616	AC003090.
HISCN94	1089	794189	1 - 748	15 - 762	N99205, Z45733, R21448, Z41991, F08373, and R36825.
HISCH73	1090	764281	1 - 428	15 - 442	T47686, and AC002540.
HISCG55	1091	731544	1 - 1082	15 - 1096	R60500, R51735, AA172114, T75381, R15141, AA071092, Z44839, R19343, R17183, T81113, F13126, and F08456.
HISCF69	1092	882055	1 - 444	15 - 458	AA577894, and AC000394.
HISCF31	1093	950628	1 - 528	15 - 542	AA702220, AA479257, AA368376, AA994157, AI149829, AA288015, AI655778, AA578960, AI363260, AA313639, and AF159423.
HISBZ83	1094	781018	1 - 420	15 - 434	AA251146, AA814335, AI610252, W60485, and AA769297.
HISBW78	1095	840252	1 - 360	15 - 374	F25526, and F18421.
HISBV60	1096	740184	1 - 394	15 - 408	AA079064.
HISBV54	1097	729356	1 - 353	15 - 367	AA180431.
HISBU75	1098	767166	1 - 486	15 - 500	W76299.
HISBS95	1099	795748	1 - 470	15 - 484	AA194042, AA447660, AA410258, AA194200, and AL121973.
HISBM13	1100	656325	1 - 480	15 - 494	N34592, T93756, and AL049776.
HISBM08	1101	959051	1 - 451	15 - 465	AI828504.
HISBK58	1102	735838	1 - 857	15 - 871	H04554, and R39715.

HISBH79	1103	774837	1 - 412	15 - 426	AI879992, T53479, AI815829, T53480, AI929243, AA723489, AA676874, AA137268, AA283262, AL135017, AA205857, and AP000356.
HISBE17	1104	662758	1 - 382	15 - 396	N44126.
HISBE11	1105	966736	1 - 371	15 - 385	AI188045, and AF207955.
HISAV01	1106	857530	1 - 263	15 - 277	AA569212.
HISAU80	1107	775438	1 - 529	15 - 543	H93319, H55789, N59118, and R89238.
HISAU79	1108	774728	1 - 129	15 - 143	AI142134, AI547295, AL038838, AL037343, AL038983, AL037436, AL037335, AL037323, AL037727, AL037443, AL038532, AL134524, AL134110, AL044125, AL037295, AL040193, AL037435, AL038822, AL044162, AL041347, AL043496, AL047012, AL043923, AL043814, AL041238, AL044186, AL040617, AL038761, AL043845, AL040463, AL047170, AL044037, AL041635, AL040294, AL044064, AL041459, AL041577, AL043538, AL040621, AL047219, AL040576, AL040625, AL045684, AL041752, AL045753, AL046850, AL040768, AL046994, AL046914, AL040052, AL040464, AL047163, AL040444, AL040510, AL043467, AL043677, AL040839, AL043492, AL041602, AL044074, AL041730, AL041523, AL043627, AL047183, AL041374, AL043848, AL043570, AL040472, AL042135, AL041324, AL045328, AL046442, AL041133, AL041098, AL045671, AL041955, AL045817, AL039316, AL040075, AL040322, AL042898, AL046392, AL039360, AL040119, AL041246, AL041096, AL044272, AL044258, AL045327, AL042096, AL041163, AL041168, AL044199, AL041159, AL041296, AL045920, AL040149, AL040148, AL047057, AL049018, AL039643, AL041086, AL040458, AL044187, AL041358, AL041292, AL045990, AL040571, AL041346, AL041142, AL040332, AL037341, AL039338, AL043941, AL041233, AL079878, AL040529, AL041197, AL046330, AL044274, AL040745, AL040370, AL079852, AL040128, AL038651, AL040553, AL047036, AL040342, AL041186, D29033, AL040414, AL045989, AL039744, AL041277, AL044201, AL040285, AL040155, AL040091, AL044165, AL046327,

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HISAU67	1109	751386	1 - 300	15 - 314	
HISAU07	1110	952941	1 - 283	15 - 297	
HISAT10	1111	964340	1 - 407	15 - 421	
HISAR89	1112	786749	1 - 480	15 - 494	AA557886.
					AI653719, AA234693, AA626351, AA234101, N62893, AA398188, AA417347, AI214856, Z40229, and AA417343.
HISAO95	1113	973368	1 - 410	15 - 424	AC006480.
HISAO49	1114	722310	1 - 364	15 - 378	T52944.
HISAL91	1115	790044	1 - 438	15 - 452	AW177681, H26816, and AB007960.
HISAH27	1116	682899	1 - 747	15 - 761	R62357, and AI744691.
HISAG10	1117	964526	1 - 455	15 - 469	N64044, and N63251.
HISAF02	1118	917357	1 - 624	15 - 638	AI357039.
HISAE12	1119	949195	1 - 664	15 - 678	H29226, R19050, R15031, AW363245, Z42156, and AF131818.
HISAD14	1120	658409	1 - 574	15 - 588	R14811, Z44371, F06803, H29207, D30932, AI912232, AA223742, and AC006359.
HISAB77	1121	772155	1 - 373	15 - 387	AA508036, AA525293, H48767, AA176604, AI918419, AA515728, H07953, AA845848, AA828047, T74524, N71033, AW102811, AA845659, AC002312, AL050321, AB003151, AF111168, AL031274, AC003663, AC005755, AL049780, Z97056, AC006449, Z84480, AP000501, AF165926, AL022326, Z93017, AL049872, AC004797, AL049569, AL109801, AC006965, U91326, AC005486, Z98051, AL133244, AP000689, AF207550, AL033527, AC005632, AL133448, AL022316, AC006530, AP000500, AC005225, AC006077, AC004883, AL034429, AF001548, Z93023, AC005104, AC007055, D87675, AL050307, AC002527, AC004815, AC004967, AP001137,

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HISAB69	1122	755024	1 - 366	15 - 380	AL133061, and AB023173.
HISAB54	1123	728915	1 - 576	15 - 590	T74508, H23061, F12474, T08527, F13291, and AF052116.
HISAB52	1124	727115	1 - 330	15 - 344	
HISAB28	1125	686621	1 - 314	15 - 328	
HISAB08	1126	959335	1 - 421	15 - 435	
HICAC35	1127	707170	1 - 455	15 - 469	N32412, and R21550.
HHNAC01	1128	913646	1 - 710	15 - 724	AA176633, and AA309418.
HHNAB42	1129	714097	1 - 141	15 - 155	AA309346, W96229, AA013298, AA057218, and Z58774.
HHLAB49	1130	723222	1 - 481	15 - 495	W03882, AA309231, and AC006360.
HGODA23	1131	675097	1 - 593	15 - 607	AA346241, W69904, F30068, AA494263, AA654661, AA837035, AL244127, AA833896, AA833875, AA568494, AL042635, AW023990, AA594072, AL345366, AL310873, AA477103, AL88468, N57739, AW148507, N58329, AA746726, AA984114, AA489571, AA721645, AL354388, AL783581, AL580250, AA224238, AL908575, AL270019, AA078381, AA365413, AA454177, AA569586, F16352, AL754567, AL755214, AL753488,

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HGBID78	1132	772814	1 - 451	15 - 465	T56492, AI922817, AI590848, AI679031, AI499934, and AF131822.
HGBHW16	1133	662148	1 - 371	15 - 385	R33570.
HGBHV89	1134	787037	1 - 655	15 - 669	N42616, and N30483.
HGBHO02	1135	954417	1 - 474	15 - 488	AA195460, AW194700, AA358473, W01427, R21613, and AA158657.
HGBHM39	1136	705606	1 - 469	15 - 483	W03202, AP000272, and AP000104.
HGBHM18	1137	854310	1 - 421	15 - 435	AI041832, and AW134713.
HGBHK55	1138	713512	1 - 596	15 - 610	N42908, N47929, AA844713, AA133450, AW104451, AW183932, AA312942, AL038022, AL038036, AI809477, N50618, AW369731, D60618, and AF000145.
HGBHG78	1139	942445	1 - 891	15 - 905	AI092570, AL120738, H55444, H11873, AW293410, AB018310,



HGBHE82	1140	780030	1 - 294	15 - 308	and AL096766.
HGBHE68	1141	753200	1 - 542	15 - 556	R25687, T27119, and R11760.
HGBHD89	1142	493910	1 - 538	15 - 552	R96539, and H62766.
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HGBHD52	1143	812643	1 - 316	15 - 330	R91640, AI092347, AI088273, AI246047, AI802088, AI863646,

HGBHB27	1144	950174	1 - 938	15 - 952	AI972041, AI924373, AI654407, AW027022, AI684361, AA810774, AA883596, AA262757, AI813282, and T57786.
					AI421699, AI421808, AA906877, AI128103, AA701448, AI085893, Z19454, AW173524, D79941, AW022173, D79805, D79605, N67509, N55943, AF114494, AF162707, AF114493, and AF162706.
HGBGZ03	1145	924788	1 - 429	15 - 443	AA284803, AI761207, F30461, F36519, and W04853.
HGBGP21	1146	671194	1 - 580	15 - 594	AI609832, W90540, AW002973, AI651483, W90579, and AC008123.
HGBGM71	1147	576919	1 - 532	15 - 546	N23258, AI680868, AI167816, AA614270, and AW134472.
HGBGL83	1148	638178	1 - 635	15 - 649	AI732503, AI791459, AW238953, AA625448, AL046586, AI290035, F00813, AC003010, AC005102, AC003102, AC005015, AC000035, AC020663, Z82171, AC000105, Z98044, AL035455, AC004032, L11910, AF053356, AL022398, AC002132, AL049553, AC000025, AL080243, AP000497, AC006537, AC004816, AP001053, AC005954, AC005726, AC005527, AL079295, AL022330, AC005777, AC005778, AL035633, AC022517, AC003998, AC006930, AC005529, AF024533, AC005624, AP001052, AC005913, AC003963, AF001549, AC004383, AL109628, AC005783, AC006581, AC005823, and AL035659.
HGBGL35	1149	707128	1 - 608	15 - 622	T55980, AA194035, and AC005385.
HGBGL19	1150	671668	1 - 448	15 - 462	H90460, W27081, and AF129926.
HGBFP63	1151	745487	1 - 485	15 - 499	H87807, AA504385, W01837, W78967, W80389, AW391522, AI371996, AI978586, AI954703, AA019304, N31025, AW444667, AW452456, AA629143, N39708, N23556, and N25494.
HGBEX85	1152	784518	1 - 557	15 - 571	W52944, AI378222, and AI473282.
HGBEX74	1153	765894	1 - 522	15 - 536	T88970, T96734, and AA011421.
HGBDY85	1154	784615	1 - 420	15 - 434	AA256145, AA482282, and AA768146.
HGBDU06	1155	960558	1 - 514	15 - 528	AA769615, AI139809, AI378329, AI342029, AI301488, AI826441, AA610474, AA975684, AA884572, and AA918024.
HGBDM36	1156	707917	1 - 533	15 - 547	AA251858, AA251857, and AA345981.
HGBDL39	1157	710349	1 - 587	15 - 601	H90452, H90399, AA345767, and C21294.

HGBDG15	1158	660743	1 - 359	15 - 373	AA191256.
HGBDG11	1159	964929	1 - 312	15 - 326	AI653506, and AC007938.
HGBCU53	1160	871948	1 - 417	15 - 431	AA115894.
HGBCS41	1161	711528	1 - 305	15 - 319	W73880, and AA449049.
HGBBP65	1162	753956	1 - 635	15 - 649	N36597, and AA345279.
HGBBG33	1163	702930	1 - 772	15 - 786	AA041218, AA344880, AI378523, AA040782, and AC007450.
HGBBA50	1164	578669	1 - 444	15 - 458	H93331, and AA344871.
HGBAJ77	1165	772756	1 - 383	15 - 397	AA159005, and AA343739.
HGBAI59	1166	868249	1 - 650	15 - 664	T60274, and AA343836.
HGBAC26	1167	790172	1 - 541	15 - 555	H50882, and AA343635.
HGAMC08	1168	958490	1 - 339	15 - 353	AA515512, and AC008174.
HFVKC87	1169	886358	1 - 757	15 - 771	C14389, D80253, D80366, D59859, D51423, D57483, D80166, D81030, D59889, D59619, D80210, D51799, D80240, D80038, D58283, D80188, D59275, D80212, D80022, C14331, D80024, D80195, D80219, D59467, D80391, D80164, D80043, D59787, D80227, D59502, D59610, AA305409, D80196, C15076, D59927, D80269, D51022, D50979, D80193, D50995, D80241, D80378, AW177440, D51060, AA305578, C14429, D80522, D80251, D80045, C75259, AW179328, T03269, AW178893, D80248, C14014, D81026, D58253, AA514188, AW378532, D80134, AA514186, D80133, AW178762, AW177501, AW177511, D51250, AW360811, AW178775, C05695, AW369651, D80268, AW352117, AW176467, AW375405, AW377671, AI910186, F13647, D51079, AW352158, D80949, D80132, AW366296, AW360844, AW360817, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, D80168, AW177505, D81111, D80439, C14298, C14227, D59373, D80064, D80302, AI905856, AW352171, AW377676, AW178906, AW352170, AW177731, AW178907, AW179019, AW179024, D80247, AW360841, AW179020, C14407, AW178909, AW177456, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, Z21582, AW352174, AW378540, T11417, AW179004, D80157, AW179012, D51103, AW178914, AW378525, AW360834, D51759, AW367967, AW177722,

					AW177728, AW179009, AW178774, AW178911, AW378543, AW352163, D58246, AW177723, AA285331, D51097, C14077, AW178983, AW352120, AW178781, D58101, T48593, D59503, D45260, AI557751, C06015, D59653, D80014, C14975, D59627, H67854, AW177508, D80258, AI535850, AW378533, AW367950, C03092, H67866, D51213, AW177497, AA809122, D60010, AW178986, AI525923, AI525917, D51231, D80228, D50981, D51221, AW177734, D59474, T03116, AI525222, D59317, C14973, AI525920, C14344, D45273, AI557774, AA514184, C14957, AI525235, AI535686, D59551, D60214, AI525227, C14046, AI525912, AI525242, AI525215, T03048, AW378542, AI525925, AW378539, C05763, T02974, C16955, Z33452, AI535961, Z30160, AW360855, AI525237, D51053, H67858, A62298, AR018138, AJ132110, A84916, A62300, AR008278, AF058696, X67155, Y17188, AB028859, D26022, A25909, A67220, D89785, A78862, D34614, D88547, Y12724, I82448, X82626, AR025207, AR060385, A82595, AR016808, A94995, AB002449, AR008443, X68127, I50126, I50132, I50128, AB012117, I50133, AR066488, AR016514, AR066482, AR060138, A45456, A26615, AR052274, A85396, A44171, Y09669, A85477, A43192, A43190, AR038669, I19525, A86792, AR066490, AR066487, AR054175, A30438, AR008277, AR008281, X93549, I18367, D88507, I14842, D50010, Y17187, A63261, AR008408, X64588, AR062872, A70867, I79511, AR016691, AR016690, U46128, D13509, A64136, A68321, AR060133, AF135125, U79457, AF123263, AR032065, X93535, and AR008382.
HFVJW07	1170	951883	1 - 504	15 - 518	AA479489, AA426174, and AA644508.
HFVIP01	1171	914567	1 - 352	15 - 366	AL134860, AA974417, AI654691, AI969350, D83780, AP000029, and AR016238.
HFVID84	1172	783129	1 - 482	15 - 496	R60730, AI378536, and AL034371.
HFVID08	1173	959739	1 - 504	15 - 518	AI652763, AI637934, and Z58900.
HFVIC84	1174	783131	1 - 505	15 - 519	N80824, AA772353, AA678493, AI817455, H06525, AI089765, W90756, W85765, AI422410, AA705876, H05093, AW044213, H43423, AI375338, AA769792, AI378819, AW023286, and

						AL080199.
HFVIC30	1175	881306	1 - 464	15 - 478		T68667, H56313, and AF097518.
HFVHX74	1176	854533	1 - 397	15 - 411		AA192391.
HFVHU23	1177	676060	1 - 683	15 - 697		AA193508, AA909248, and AI271531.
HFVHR05	1178	932181	1 - 535	15 - 549		AL046172, H59509, and H23797.
HFVHQ93	1179	792444	1 - 498	15 - 512		T83742, and AA135378.
HFVGY60	1180	710929	1 - 301	15 - 315		AA829531, AP000154, and AP000012.
HFVGM12	1181	971182	1 - 316	15 - 330		R68859, AI217090, AA381194, AA299087, AA828662, AA491438, AA828588, AI348780, AA828569, AA947364, AA508418, AI613419, AA653823, AI400912, AA299351, AL042753, AI867386, AA523490, AA626637, AW008062, AI697369, AI887768, AI799421, AA226260, AW439724, AI693478, AI914151, AI951436, AA160566, AW169469, AL133861, AA493667, AA164356, AA228442, AW167267, AA070240, AW078552, AW193493, AA564753, AA169768, AA365688, AA780648, AL039958, AA167179, AI292085, AI264046, AA339079, AW166968, AA658360, AI298710, AI075266, AI038990, AI298079, AI610634, AA744449, AA744465, AA745470, AA714595, H91358, AW440662, AI338806, AA633039, AC002477, AJ003147, AC004831, AC004148, AC004107, AC004398, AC006323, AC006026, AC007395, AC007278, AL133246, AC004167, AF111168, AF088219, AC000379, AC002301, AL022476, AC002418, Z83843, AC004386, AL035417, AL031775, AL035603, AC001643, AC002319, AC005043, D86991, AC000051, D87002, AC007204, AC012331, AC002308, AP000356, AC002094, AL096712, AC003681, AC004493, AC004223, AC007285, AL021938, AC005562, AC004220, AL035070, AC008040, AC005544, AL031734, AC007021, AC005800, AC007226, D86995, AL035410, AL035685, U91323, AP000555, AC007052, AB033094, AC005781, AC007686, AC002312, AL133321, AP000128, AP000206, AL035530, AL008583, AP000245, AL133371, AC003986, AC006966, AF064861, AL008708, AC004232, AC005621, AL035659, AL035420, AC013417, AC004655, AB020863, AC007436, AC007656, AL080243,

					AC005037, AC005523, Z69714, AC004500, AC005875, AC004765, Z96622, AJ246003, AL022339, AC006071, AC005300, AC002115, AC004841, AC004491, AC006946, AF109907, AC004000, AC008981, AL031280, AC004188, AC005288, AF196969, AP000302, AC004209, AP000114, AP000046, AP000514, AP000067, AC004534, AF042484, AL121658, U29874, D87004, M64554, AL080242, AC005613, AC006974, Z84477, AC004854, AL122021, AC005924, AC002400, AL031427, AC005747, AL031591, Z83840, AC004629, AC006275, and Z93023.
HFVBA27	1182	414543	1 - 787	15 - 801	AI114725, N58282, H67798, R83539, N77653, AA972043, AA005004, H68072, AI298350, AA343394, AI133372, and H71687.
HFLVG70	1183	757521	1 - 443	15 - 457	W87617.
HFLUE23	1184	676425	1 - 394	15 - 408	T84238.
HFLUE22	1185	522779	1 - 209	15 - 223	
HFLUD68	1186	753847	1 - 518	15 - 532	AA007365.
HFLQJ68	1187	753216	1 - 368	15 - 382	H81620, and T91378.
HFLQJ38	1188	709034	1 - 343	15 - 357	T81723, T84581, R99474, R28738, T82031, T78557, and AF209192.
HEPNE51	1189	855589	1 - 558	15 - 572	N99018.
HDRMD24	1190	676826	1 - 366	15 - 380	H83014, R58919, and F04570.
HDRMA68	1191	785478	1 - 427	15 - 441	H39778, H43264, AW074003, AI923864, AI571406, AI865582, AI740509, AI087861, AW027054, AW025858, AW328432, AI129952, AI345992, AW135872, AA781441, AA769447, AA742292, AI969997, AA946657, AA811514, AA527064, AW134596, AI633572, AW136628, AW009874, AA451698, AW243885, AA774271, AI818126, F37014, AI092084, AI992065, AI928446, AI475650, AI143876, AI143870, F33207, AA741257, AI129921, F21628, AW166911, AA063520, AW105702, AA716235, AA736768, AW368798, AA910938, AW328431, AI453599, AI223368, AW368800, AA192190, AW363815, AI198728, AI864067, AA194558, W23913, and AA769417.

HDRMA04	1192	927372	1 - 741	15 - 755	AA147884, AI342382, AW083160, AI983005, AW263262, AW338006, AI814345, AW204200, AI347990, AA045008, T54850, and AA147491.
HDDAF49	1193	911314	1 - 307	15 - 321	AL133047.
HDDAE06	1194	954683	1 - 524	15 - 538	H38912, and H67466.
HDDAC56	1195	733673	1 - 442	15 - 456	R78606, and AL037446.
HDDAC11	1196	840301	1 - 415	15 - 429	R76361.
HDDAB07	1197	954150	1 - 345	15 - 359	AA639313, AL022717, and AA937864.
HCYBO59	1198	520114	1 - 407	15 - 421	AA305759, AI648536, AI870450, H53564, AW364689, AW168274, AI915135, H53563, H61027, AI252294, AI054391, AW304586, AI053974, N49703, AW271152, AW302049, AA342004, AI085785, H53538, C14331, C14429, D80166, C14389, C15076, D58283, D80022, D59927, D59502, D80043, D80227, D51799, D59859, D59467, D80195, D51423, D59619, D81030, D80210, D80391, D80164, D59275, D80240, D80253, D59787, D50995, D80212, D80269, D80196, D80188, D80219, AA305409, D50979, D57483, D80366, D80038, D59889, D80193, D80378, D59610, D80024, D80241, D80045, C14407, D51060, D51022, T03269, AW178893, AW177440, AA305578, C75259, AW179328, D80134, C14014, AW378532, D81026, AA514188, D80248, AW178775, AW369651, D80251, D80522, AW178762, F13647, D51250, AI910186, D80168, D58253, AW177501, AW177511, AA514186, D80133, AW360811, AW352158, D80132, AW352170, C14227, C05695, AW352117, AW176467, AW375405, D81111, C14298, D80268, AW377671, D80064, AI905856, AW366296, AW360844, AW375406, AW360817, AW378534, D59373, AW179332, AW377672, AW179023, AW178905, Z21582, D80247, AW378540, D80302, AW352171, D80439, AW377676, AW178906, AW177505, AW177731, AW178907, AW179019, AW179024, D51097, T11417, AW179020, AW352174, AW360841, AW178909, AW177456, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, AA285331, AW360834, D51103, AW179004, AI557751, AW179012, AW367967, AW178914, AW378525, D80157, AW177722, AW177728, C14077, D58101,



					AW179009, D51759, D59503, AW178774, AW178911, AW378543, AW352163, AW179220, D58246, C14344, AW178983, AW352120, D80014, AW178781, T48593, C06015, D59627, C03092, AW177508, AW177723, D59653, D80258, AI535850, C14975, D45260, D51213, AW378533, AW367950, H67866, AA809122, AW177497, H67854, D80228, AI535686, AI557774, AW178986, AI525923, T03116, AI535961, D45273, T02974, D51231, AW177734, AI525917, D59317, AI525912, C14973, D60010, D51221, AI525920, D59474, T03048, AA514184, C14046, D59551, C14957, D60214, AI525227, AF006514, A62300, A84916, A62298, AJ132110, AR018138, AF058696, X67155, Y17188, D26022, A25909, AR008278, A67220, D89785, A78862, D34614, AB028859, D88547, X82626, Y12724, AR025207, A82595, A94995, AR060385, AB002449, AB012117, AR008443, AR066482, X68127, I50126, I50132, I50128, I50133, A85396, A44171, A85477, U87250, AR066488, I19525, AR016514, A86792, AR060138, A45456, A26615, AR052274, X93549, AR066490, Y09669, A43192, A43190, AR038669, AR066487, I18367, AR054175, A30438, D88507, I14842, D50010, Y17187, A63261, AR008277, AR008281, AR008408, AR062872, A70867, AR016691, AR016690, U46128, AF135125, D13509, A64136, A68321, AR060133, I79511, U87247, AB033111, U79457, AF123263, X93535, AB023656, AR032065, AR064240, and AR008382.
HCBYBL79	1199	888275	1 - 462	15 - 476	AA922273, AI218568, AA305614, AI077416, N67108, AW000975, AI080088, AW270427, AW268569, AI312095, AI472929, R34604, and AI021920.
HCRQB03	1200	922880	1 - 533	15 - 547	AA568716, AW449659, R44623, AA460549, AI351558, AI809818, R92007, AI886414, AI245405, H95380, AA743742, AI783561, AW243862, AA632360, AA506121, AA811920, AI734201, AA501649, AC003960, AC002540, AC005082, AC004477, AC007395, AC009516, AF196969, AC000120, AC004126, AC007011, AC004033, AC007731, AC005500, AP000432, AB023049, AF001549, AC003035, AC002426, and AC007130.

HCRPQ40	1201	881408	1 - 656	15 - 670	AI817642, AI689047, AI208335, AA878428, AW450426, AA469160, H92073, AA469161, AA482940, AA171728, AA425285, W45360, AW242060, AI587648, AI619496, AI952227, AI587188, AI699819, AA911674, AI952480, AW275824, AA642893, AI269458, AI698520, AI888262, AI394549, AA031518, AI969614, AW118691, AI284498, AI753871, AI920801, AA625676, AW073829, AA732340, AA873305, AI282233, AW243745, AI266144, AI923244, AA804446, AA233919, AI689027, AW014369, W33158, AA173171, AA857122, AA971825, AW438570, AI745482, AW081987, N78892, N72081, AI318399, AI244531, AA028932, AI674601, AI264459, N34434, AI357346, AA524134, C05912, AI039387, AI281999, AW268377, AI347595, AA526733, AA587489, AI003780, AA593927, AI285454, AI8666346, AI432966, AA620322, AI538092, C05822, AA580607, AA902766, AA999791, AI289778, AI004284, AA773432, R40653, AI041163, C05783, AW118245, AI811394, AI038446, AI758393, H92123, AW130927, AI207700, AI202520, AI151374, W78172, AA653384, AI680368, AI184262, AI985324, AI301547, AI890515, AW051805, AI245634, AI157835, AI985603, AW193115, AI589409, DI9685, AI697319, AI679231, AI679808, AI073919, AI369852, N74461, AA126449, AI684312, AI950695, AA447084, AI042116, T34717, AA628448, AA463891, H15421, F10166, AA164596, AI620027, AI471088, Z38930, AA576917, AI360744, AA101171, AI934234, AI800825, AW023962, AA670056, AW183764, AA614832, AA001197, R23243, H02773, AW131908, AA284761, AA476282, AI420910, AA533892, AI811368, AI679809, AA902495, N63998, W65422, AA508153, AA662794, AA759338, AW082154, AA779581, AI432564, AI954929, AI263036, AI287506, AW150468, H42487, R79704, AI245097, AI866355, AI671650, AI689273, AW050398, AI192070, AI784260, H06866, AW149912, R41968, AA402619, AA402555, H95957, AI750338, AA360537, AA357362, T85100, T10709, AA719452, AI933485, AA234168, AW166325, AW196186, AI696438, C02110, AA284762, AA292691,
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HCRPE30	1202	910021	1 - 110	15 - 124	AA494213, and AA433814.
HCROA43	1203	948286	1 - 797	15 - 811	AB014604, and AC003093. Z99396, AL038837, AL037051, AL036725, AL036418, AA631969, AL039074, AL036924, AW392670, AL039564, AL039085, U46350, AL036858, AL039156, AL039108, AL039109, AL038509, AL039128, AL037094, AL039659, AL038531, AL119457, AL036196, AW384394, AW363220, AW372827, AL039625, AL039648, AL119522, AL045337, AL119497, AL119319, AL036767, AL038447, AL037082, AL119391, AL037526, AL037639, AL036190, AL119443, AL119324, AL039678, AL039629, AL119363, AL119484, AL039423, AL036238, AL039150, AL040992, AL038520, AL042909, AL119483, U46351, AL119355, AL119496, U46346, U46341, U46347, U46349, AL037077, AL119418, AL119341, AL119335, AL038851, AL134524, AL119396, AL037726, AL039386, AL036268, AL039410, AL119439, AL037085, AL119444, AL037205, AL036998, AL037615, AL134902, AL037178, AL036733, AL042965, AL119401, AL134527, AL134538, AL036679, AL042542, AL042614, AI142134, AL036191, AL037027, AL119399, AL042984, AL042975, AL045353, AL036765, U46345, AL043003, AL119488, AL042544, AL036719, AL043019, AL036973, AL042551, AL043029, AL042450, AL037054, AL037021, AL119464, AL036774, AL036836, AL036158, AL036999, AL036886, AR066494, AR060234, AR023813, A81671, AR064707, AR069079, AB026436, and AR054110.
HCRNR03	1204	922819	1 - 748	15 - 762	AI025752, AI031574, AA488791, Z44604, AA007253, AI652016, and AW296312.
HCRND06	1205	934631	1 - 601	15 - 615	AI521755, AI038605, AA969113, AA913828, AI377005, AI261324, AW052138, AI474795, Z39645, AI636293, AI807319, R36992, AI348623, AI699951, AI239432, AL134524, AL045328, AL042898, AA923073, AL038838, AL037343, AL038983, AL037436, AI142134, AL037335, AL037323, AL037443, AL037727, AL038532, AL038761, AL047012, AL044125, AL038822, AL037435, AL040193, AL044162, AL041347,

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HCRMX10	1206	963663	1 - 669	15 - 683		AI074053, AI733195, AI793125, AI805776, and AA937728.
HCRMG11	1207	965918	1 - 437	15 - 451		AA400298, AA401412, AI243657, AI214420, AI698759, AL119457, AA885403, AL042544, AL042382, AL119399, AL079794, AI624279, AL049085, AL042745, AL079977, AW082113, AL045266, AL040243, AL119748, AL045500, AI491852, AW087445, AI610362, AI269862, AI801325, AI500662, AI284517, AI499285, AI499463, AI275175, AI796743, AL039276, AI433976, AI433157, AI539771, AL043326, AI537677, AI500659, AI500523, AI500706, AI491776, AI445237, AW151138, AL042628, AI633493, AI917055, AL079963, AL041862, AL037081, AI284484, AL042551, AI538716, AI802542, AI648509, AW170635, AI364788, AI345416, AI432666, AW080402, AI872545, AW071349, AA225339, AI284509, AL079741, AI815232, AI620284, AW132056, AI886753, AI815855, AI036403, AL036361, AI499381, AL042744, AI890833, AI926790, AI281772, AI889133, AL040097, AW059713, AI440239, AW104724, AI654276, AW051258, AI637584, AI559296, AI862139, AW301505, AL119324, AI564719, AI560099, AI619502, AI677796, AI335449, AI269205, AW026882, AI702068, AI624084, AL039086, AW262565, AI433037, AI702073, AI436456, AI624206, AI682841, AW008048, AI345612, AI955917, AI696612, AI567940, AI274508, AI432656, AI476046, AL042538, AI431975, AI889376, AL037454, AL038605, AL045163, AI524671, AI612913, AI921248, AI632408, AI684279, AI873644, AI863014, AI783504, AI499512, AI567993, AI349598, AI922901, AI289937, AI874261, AW302988, AL121365, AI648663, AI611738, AI872711, AI633125, AL045620, AL046931, AI521012, AL043981, AW071417, AI434223, AL042787, AI633330, AL041772, AI610402, AI819976, AI816010, AI620003, AI580435, AL121270, AI308035, AI623396,

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HCQDE22	1208	949991	1 - 733	15 - 747	AA677543, N58518, AA699859, and AC006556.
HCQDA13	1209	908299	1 - 435	15 - 449	H77767, R89164, and AA995737.
HCQCQ76	1210	953491	1 - 816	15 - 830	AA418408, AW237234, N45214, AI081797, AW293817, and AA927507.
HCQAC71	1211	951844	1 - 483	15 - 497	AA401242, AI609152, AI078381, AA102778, AI198283, AI077572, AI694848, AI201085, AA215665, AA978209, AA446587, AA114156, AW016425, AI818924, AI277223,



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HCNSR78	1212	773818	1 - 178	15 - 192		N78194.
HCNSR32	1213	699694	1 - 446	15 - 460		R80459, and R38126.
HCNSE03	1214	925492	1 - 823	15 - 837		AA489166, AI339427, AA807127, AW241274, AI365109, and AA700583.
HCNDV73	1215	764119	1 - 382	15 - 396		AA837403, and AA019730.
HCNDV41	1216	862324	1 - 439	15 - 453		AA602473.
HCNDK37	1217	706359	1 - 472	15 - 486		W74405.
HCNDF65	1218	747499	1 - 424	15 - 438		R09546.
HCNDB86	1219	785168	1 - 512	15 - 526		AW009761, AI688403, and T98293.
HCNCX91	1220	789556	1 - 177	15 - 191		T67235.
HCNCX27	1221	682479	1 - 470	15 - 484		T92888, and AA669377.
HCNCT03	1222	923344	1 - 462	15 - 476		AI281597.
HCNCO59	1223	738889	1 - 403	15 - 417		H91161.
HCNCM79	1224	892693	1 - 473	15 - 487		AA533959, AI948903, AI983767, AI832391, AI831407, AI833297, AA587764, AW134688, AI304380, AI813445, AI283185, AA938765, AI336470, AA857922, AI339648, AW206923, AI832498, AI744428, AI833021, AI336626, AA534511, AI732376, AI732377, AI285352, AI864896, AA422086, AW361498, AW361500, AW361502, AI766378, AI246768, AI833288, AW351854, AA535314, AW361503, AA422178, AI720988, T25111, AA283751, and AW351839.
HCNCF19	1225	668043	1 - 452	15 - 466		H73183, AW378939, AI242654, AI083578, AA203154, AI266074, and AA708327.
HCNAZ20	1226	670031	1 - 327	15 - 341		R85819, AI732227, AA572686, and AA579567.
HCNAY45	1227	716992	1 - 610	15 - 624		H85187, AA570563, H63548, H84654, HI7549, AI971577, R83433, and AC006481.
HCNAT92	1228	518899	1 - 334	15 - 348		AI796024.
HCNAT67	1229	508295	1 - 260	15 - 274		N38991, AA728939, AA715348, AC006509, AC002350, AL031311, AF190465, AL021937, AP001050, AC005089, AC006160, AC005778, AL022721, AP000104, Z82172, and

HCNAQ26	1230	685199	1 - 570	15 - 584	AC003026.
HCNAP29	1231	855685	1 - 441	15 - 455	AA196782, and AA327410.
HCNAL30	1232	522672	1 - 114	15 - 128	AA327299, AA283045, and AC004382.
HCNAK11	1233	967945	1 - 607	15 - 621	AC004519.
HCNAA41	1234	791545	1 - 558	15 - 572	AA327226, T87318, AA699663, AA723867, and AC003991.
					AA033945, AA525921, AA524609, AA225192, AA327031,
					AA856847, R85107, AW075801, AI584030, AA873521,
					AI222713, and AC004924.
HCLHE01	1235	914341	1 - 650	15 - 664	AA576288, N31211, N21276, AA669338, and R01545.
HCIAD89	1236	786766	1 - 513	15 - 527	AI277430, AI962658, AI094792, AA984854, AW237033,
					H41285, and NS3276.
HCIAC12	1237	970750	1 - 761	15 - 775	AI821052, AI821801, AW138724, AW204165, AA877677,
					AI802637, AA493324, AW004997, AI821221, and AA483638.
HASMC23	1238	675527	1 - 234	15 - 248	N48942, and AC007879.
HAQNH18	1239	883367	1 - 548	15 - 562	R54517, R20061, R20062, and Z42566.
HAQNB68	1240	752573	1 - 725	15 - 739	N76861.
HAQMP04	1241	925685	1 - 729	15 - 743	AI632567, AI797713, and AI341397.
HAQMK53	1242	727708	1 - 532	15 - 546	H49092, AL133216, and AC006455.
HALTA38	1243	705895	1 - 474	15 - 488	AI674565, AI951211, AI924393, AA923771, AI738800,
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					AA876404, AA983837, AI300768, AW193725, AA054746,
					AA313302, D79800, T41071, T40203, C16565, C16572, and
					AL137761.
HALSD90	1244	500844	1 - 327	15 - 341	AL035703.
HALSD51	1245	500852	1 - 317	15 - 331	Z98745, and AC005678.
HALSD34	1246	509765	1 - 317	15 - 331	
HALSD03	1247	960910	1 - 396	15 - 410	
HALSC37	1248	705894	1 - 298	15 - 312	
HALSC18	1249	667044	1 - 348	15 - 362	AL038842, AA593537, AI431240, AW271904, AA659360,
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H2MCA78	1251	575194	1 - 450	15 - 464		AA257135, AA256509, N77130, and AA513537.
						AA316840, R27234, R27097, AA338978, AA126252, R27438, R26867, and AP000344.
H2MBY07	1252	953691	1 - 611	15 - 625		AA316667, and AA427653.
H2MBW43	1253	715430	1 - 362	15 - 376		AA315170, N49803, and AA694311.
H2MBW31	1254	698281	1 - 509	15 - 523		AA315158, N76067, and M89651.
H2MBH48	1255	908926	1 - 496	15 - 510		AA308569.
H2MBE37	1256	597070	1 - 583	15 - 597		AA308338, R60841, AI219925, D51799, D50979, D80188, D58283, D80227, D59610, D59502, D59859, D80166, D80253, D51423, D59619, D81030, D80210, D80240, D80269, D80164, D57483, D80212, D80022, D80195, D80219, D80241, D80391, D59275, D80043, D59787, C14331, D80378, D80366, D59889, D59927, D80196, D80024, D59467, D80038, D50995, D80193, C14389, AA305409, T03269, C15076, C75259, D80045, C14014, AW178893, D80522, D51022, AW179328, D51250, D81026, AW177440, D51079, D80268, AA305578, AW378532, F13647, D80251, D59695, D80248, D80168, D81111, D52291, AA514188, AW178762, C14227, AW352117, Z21582, AA514186, D80133, C14298, AW378540, AW360811, C14407, AW377671, AW375405, AW178754, AW366296, AW360817, AW375406, AW360834, AA285331, AW378534, AW352171, AW179332, AW377672, AW377676, AW179023, AW178905, AW179024, D80439, AW179020, D80302, AW177456, AW178906, AW177731, AW178907, AW179019, AW179018, D80247, D80014, T03116, AW378528, AW178908, AI557751, T11417, AI557774, AW352120, D80157, AW178914, AW378543, AW378525, D51103, C06015, AW178774, AW178781, AW352163, AW378539, D58101, D59503, T48593, D59627, D45260, D80258, H67854, T02974, AI525923, C03092, H67866, D51213, AW378533, AA809122, D45273, AI525920, AW367950, D80064, AW178986, AI525917, C14344, D58246, T03048,

H2MBA41	1257	711567	1 - 632	15 - 646	<p>D50981, D51221, AA514184, D59474, D59317, AW179013, C14973, D59551, Z30160, AI535686, AI525235, AW178759, AI525227, AI525237, H67858, AI525912, Z33452, AI525215, AI525242, C16955, AI525925, AW378542, T02868, AI525907, Z95115, AJ236688, AJ236699, Z59925, Z64936, A62298, A84916, A62300, AJ132110, AR018138, AR008278, D26022, X67155, Y17188, A25909, A67220, D89785, A78862, D34614, AF058696, D88547, X82626, AR025207, AB028859, Y12724, A82595, AB002449, X68127, A94995, AR060385, I50133, AR008443, I50126, I50132, I50128, AR066488, AR016514, AR060138, A45456, A26615, AR052274, A43192, A43190, AR038669, Y09669, AR054175, I14842, AR066487, A30438, Y17187, AR008277, AR008281, A63261, D50010, AR062872, A70867, AR008408, AR016691, AR016690, U46128, A64136, A68321, I79511, and AR060133.</p> <p>H41196, AI420520, AA308206, AI280930, AI940197, D51759, D59927, D51799, D80253, D80227, D80269, D80366, D80188, D80439, D59467, D59859, D80166, D51423, D59619, D80210, D80240, C14389, D80522, AA305409, D81030, D59610, C14331, D80024, D80212, D80268, D51060, D58283, D80248, D80219, D80022, D80195, D80247, D80391, D80164, D59275, D80038, D80043, D59787, D59502, D80378, D57483, D50979, C14014, D59889, D81026, AA514188, D50995, D80196, D80133, D51022, AA514186, D80251, D80157, D80241, AA305578, C15076, D80193, D80045, C75259, D80302, AW360811, T03269, AW377671, D51103, C14429, AW177440, AW178893, AW375405, AW360844, D59653, C06015, C05695, D45260, AW366296, AW178906, AW177501, AW177511, D59373, AW360817, AW179328, AW179020, T48593, AW375406, AW378534, AW352171, AW179332, AW377672, AW179023, AW178905, AW177731, AW378528, AW178762, AW178754, AW179019, AW179024, AW377676, AW378532, D80064, T03116, H67854, AW360841, AW178909, AW352120, AW177505, AI525925, AW178775, AW177456, AW179004, AW352170, D51250, AW178986, AW178907, C03092,</p>
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H2LAM15	1258	767606	1 - 895	15 - 909	<p>AA722878, AW070839, AA503095, AA889316, AA628716, AI336154, AI911886, AA918399, N89745, AI268726, AA613950, W17236, AA910620, AA626250, T97465, AA923090, AI216561, T97464, H05962, AA707375, T96140, AA314130, AI688102, AW083237, AA037564, AA722828, AI219608, R15087, AA345081, AI675972, AA932792, AA503524, T96222, AI522074, AI923674, AI338611, AA037485, AW380840, AI581541, N30008, AA445929, AA843974, N89900, AA776102, AA314811, AA385260, W19454, AW002151, AA806039,</p>

H2CBP41	1259	923006	1 - 503	15 - 517	AI870575, AA890143, and AC005971. AA307889, AA054296, W96510, AI346035, W93642, AA502752, AI130754, AA770166, AA778512, AW024473, AI056264, AW024828, T87078, AA677316, H71308, AI741867, AA034248, AI580789, AW009144, AA854351, AI452752, AW024484, AI090276, AI290993, AI857696, AI719339, AI338292, W92826, AI091503, AA460398, F26472, W16886, F36965, T87077, AI024756, AI291319, AA026293, AA814858, AA812735, AI051900, AI127750, W38862, AI076382, AA778103, AA609966, AI122824, AA074957, AI077896, AA848104, AA782993, AA205010, AI289262, AA482670, AA461350, AA026292, AI245497, AI436341, AI278737, AI283744, W93295, AA075112, T97653, AA782956, AI707753, AA718912, AW337132, AA628645, AA628261, W93902, AA873209, AA460335, H70902, AA058474, AI282039, AI758943, AA448793, F37629, N89690, AA461175, AA629835, AI567067, AI219583, T97654, AA095949, AA164705, AI805468, AA093482, AI880308, W96477, N54735, AA629883, AA629896, AA757035, AI217200, and AA585304.
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**TABLE 4**

<u>Code</u>	<u>Description</u>	<u>Tissue</u>	<u>Organ</u>	<u>Cell Line</u>	<u>Disease</u>	<u>Vector</u>
AR022	a Heart	a Heart				
AR023	a Liver	a Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a Prostate	a Prostate				
AR026	a small intestine	a small intestine				
AR027	a Stomach	a Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clonotech)	Human Lung (clonotech)				
AR057	Human Mammary (clonotech)	Human Mammary (clonotech)				
AR058	Human Thymus (clonotech)	Human Thymus (clonotech)				



AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia				
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonotech)	Prostate				

		(clonotech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil germinal center centroblast	Tonsil germinal center centroblast				
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0015	Human Gall Bladder, fraction II	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0018	Human Greater Omentum, fII remake	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0035	Human Salivary Gland	Human Salivary Gland	Salivary gland			Uni-ZAP XR
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0037	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			pBluescript
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus		disease	Uni-ZAP XR
H0047	Human Fetal Liver	Human Fetal Liver	Liver			Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0057	Human Fetal Spleen					Uni-ZAP XR
H0085	Human Colon	Human Colon				Lambda ZAP II

H0095	Human Greater Omentum, RNA Remake	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0096	Human Parotid Cancer	Human Parotid Cancer	Parotid		disease	Lambda ZAP II
H0098	Human Adult Liver, subtracted	Human Adult Liver	Liver			Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0147	Human Adult Liver	Human Adult Liver	Liver			Uni-ZAP XR
H0152	Early Stage Human Liver, fract (II)	Human Fetal Liver	Liver			Uni-ZAP XR
H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage Human, II	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0184	Human Colon Cancer, metastasized to liver	Human Colon Cancer, metastasized to liver	Liver		disease	Lambda ZAP II
H0194	Human Cerebellum, subtracted	Human Cerebellum	Brain			pBluescript
H0197	Human Fetal Liver, subtracted	Human Fetal Liver	Liver			Uni-ZAP XR
H0198	Human Fetal Liver, subtracted, pos. clon	Human Fetal Liver	Liver			Uni-ZAP XR
H0199	Human Fetal Liver, subtracted, neg clone	Human Fetal Liver	Liver			Uni-ZAP XR
H0204	Human Colon Cancer, subtracted	Human Colon Cancer	Colon			pBluescript
H0205	Human Colon Cancer, differential	Human Colon Cancer	Colon			pBluescript
H0231	Human Colon, subtraction	Human Colon				pBluescript
H0232	Human Colon, differential expression	Human Colon				pBluescript
H0246	Human Fetal Liver-Enzyme subtraction	Human Fetal Liver	Liver			Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon		disease	Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas			Uni-ZAP XR
H0316	HUMAN STOMACH	Human Stomach	Stomach			Uni-ZAP XR
H0331	Hepatocellular Tumor	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0339	Duodenum	Duodenum				Uni-ZAP XR
H0343	stomach cancer (human)	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0349	human adult liver cDNA library	Human Adult Liver	Liver			pCMVSPORT 1
H0355	Human Liver	Human Liver, normal Adult				pCMVSPORT 1
H0357	H. Normalized Fetal Liver, II	Human Fetal Liver	Liver			Uni-ZAP XR

H0379	Human Tongue, frac 1	Human Tongue				pSport1
H0380	Human Tongue, frac 2	Human Tongue				pSport1
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0436	Resting T-Cell Library, II	T-Cells	Blood	Cell Line		pSport1
H0447	Salivary gland, re-excision	Human Salivary Gland	Salivary gland			Uni-ZAP XR
H0448	Salivary gland, subtracted	Human Salivary Gland	Salivary gland			Lambda ZAP II
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSport1
H0479	Salivary Gland, Lib 3	Human Salivary Gland	Salivary gland			pSport1
H0485	Hodgkin's Lymphoma I	Hodgkin's Lymphoma I			disease	pCMVSPORT 2.0
H0486	Hodgkin's Lymphoma II	Hodgkin's Lymphoma II			disease	pCMVSPORT 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSPORT 2.0
H0489	Crohn's Disease	Ileum	Intestine		disease	pSport1
H0494	Keratinocyte	Keratinocyte				pCMVSPORT 2.0
H0506	Ulcerative Colitis	Colon	Colon			pSport1
H0509	Liver, Hepatoma	Human Liver, Hepatoma, patient 8	Liver		disease	pCMVSPORT 3.0
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver			pCMVSPORT 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line				pSport1
H0522	Primary Dendritic cells, frac 2	Primary Dendritic cells				pCMVSPORT 3.0
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas		disease	pSport1
H0542	T Cell helper I	Helper T cell				pCMVSPORT 3.0
H0574	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0575	Human Adult Pulmonary; re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0590	Human adult small intestine, re-excision	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0593	Olfactory epithelium; nasal cavity	Olfactory epithelium from roof of left nasal cavity				pCMVSPORT 3.0
H0595	Stomach cancer (human); re-excision	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0596	Human Colon Cancer; re-excision	Human Colon Cancer	Colon			Lambda ZAP II
H0597	Human Colon; re-excision	Human Colon				Lambda ZAP II
H0598	Human Stomach; re-excision	Human Stomach	Stomach			Uni-ZAP XR
H0616	Human Testes,	Human Testes	Testis			Uni-ZAP

	Reexcision					XR
H0619	Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0622	Human Pancreas Tumor; Reexcision	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0632	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver			Lambda ZAP II
H0637	Dendritic Cells From CD34 Cells	Dendritic cells from CD34 cells				pSport1
H0643	Hep G2 Cells, PCR library	Hep G2 Cells				Other
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	Papillary Cystic neoplasm of low malignant potential			disease	pSport1
H0656	B-cells (unstimulated)	B-cells (unstimulated)				pSport1
H0658	Ovary, Cancer: (9809C332): Poorly differentiated adenocarcinoma	9809C332- Poorly differentiate	Ovary & Fallopian Tubes		disease	pSport1
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576 A8)	Ovary			pSport1
H0674	Human Prostate Cancer, Stage C; re-excision	Human Prostate Cancer, stage C	Prostate			Uni-ZAP XR
H0675	Colon, Cancer: (9808C064R)	Colon Cancer 9808C064R				pCMVSPORT 3.0
H0676	Colon, Cancer: (9808C064R)-total RNA	Colon Cancer 9808C064R				pCMVSPORT 3.0
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR
S0294	Larynx tumor	Larynx tumor	Larynx, vocal cord		disease	pSport1
S0306	Larynx normal #10 261-273	Larynx normal				pSport1
S0328	Palate carcinoma	Palate carcinoma	Uvula		disease	pSport1
S0330	Palate normal	Palate normal	Uvula			pSport1
S0332	Pharynx carcinoma	Pharynx carcinoma	Hypopharynx			pSport1
S0350	Pharynx Carcinoma	Pharynx carcinoma	Hypopharynx		disease	pSport1
S0352	Larynx Carcinoma	Larynx carcinoma			disease	pSport1
S0354	Colon Normal II	Colon Normal	Colon			pSport1
S0356	Colon Carcinoma	Colon Carcinoma	Colon		disease	pSport1
S0358	Colon Normal III	Colon Normal	Colon			pSport1
S0360	Colon Tumor II	Colon Tumor	Colon		disease	pSport1
S0368	Human Pancreatic Langerhans	Islets of Langerhans				pSport1
S0370	Larynx carcinoma II	Larynx carcinoma			disease	pSport1
S0372	Larynx carcinoma	Larynx			disease	pSport1

	III	carcinoma				
S0374	Normal colon	Normal colon				pSport1
S0376	Colon Tumor	Colon Tumor			disease	pSport1
S0378	Pancreas normal PCA4 No	Pancreas Normal PCA4 No				pSport1
S0380	Pancreas Tumor PCA4 Tu	Pancreas Tumor PCA4 Tu			disease	pSport1
S0382	Larynx carcinoma IV	Larynx carcinoma			disease	pSport1
S0384	Tongue carcinoma	Tongue carcinoma			disease	pSport1
S0392	Salivary Gland	Salivary gland; normal				pSport1
S0394	Stomach;normal	Stomach; normal				pSport1
S0404	Rectum normal	Rectum, normal				pSport1
S0406	Rectum tumour	Rectum tumour				pSport1
S0408	Colon, normal	Colon, normal				pSport1
S0410	Colon, tumour	Colon, tumour				pSport1
S0430	Aryepiglottis Normal	Aryepiglottis Normal				pSport1
S0432	Sinus piniformis Tumour	Sinus piniformis Tumour				pSport1
S0434	Stomach Normal	Stomach Normal			disease	pSport1
S0436	Stomach Tumour	Stomach Tumour			disease	pSport1
S0438	Liver Normal Met5No	Liver Normal Met5No				pSport1
S0440	Liver Tumour Met 5 Tu	Liver Tumour				pSport1
S0442	Colon Normal	Colon Normal				pSport1
S0444	Colon Tumor	Colon Tumour			disease	pSport1
S0446	Tongue Tumour	Tongue Tumour				pSport1
S0448	Larynx Normal	Larynx Normal				pSport1
S0450	Larynx Tumour	Larynx Tumour				pSport1
S0456	Tongue Normal	Tongue Normal				pSport1
S0464	Larynx Normal	Larynx Normal				pSport1
S0466	Larynx Tumor	Larynx Tumor			disease	pSport1
T0008	Colorectal Tumor	Colorectal Tumor			disease	pBluescript SK-
T0023	Human Pancreatic Carcinoma	Human Pancreatic Carcinoma			disease	pBluescript SK-
T0090	Liver, normal					pBluescript SK-
T0091	Liver, hepatocellular carcinoma					pBluescript SK-
T0109	Human (HCC) cell line liver (mouse) metastasis, remake					pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake					pBluescript SK-
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake					pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line					pBluescript SK-
L0005	Clontech human aorta polyA+					

	mRNA (#6572)					
L0015	Human					
L0021	Human adult (K.Okubo)					
L0022	Human adult lung 3" directed MboI cDNA					
L0040	Human colon mucosa					
L0109	Human brain cDNA	brain				
L0138	Human normal gingiva	normal gingiva				
L0142	Human placenta cDNA (TFujiwara)	placenta				
L0143	Human placenta polyA+ (TFujiwara)	placenta				
L0157	Human fetal brain (TFujiwara)		brain			
L0356	S, Human foetal Adrenals tissue					Bluescript
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0364	NCI_CGAP_GC5	germ cell tumor				Bluescript SK-
L0365	NCI_CGAP_Phe1	pheochromocyto ma				Bluescript SK-
L0367	NCI_CGAP_Sch1	Schwannoma tumor				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0371	NCI_CGAP_Br3	breast tumor	breast			Bluescript SK-
L0372	NCI_CGAP_Co12	colon tumor	colon			Bluescript SK-
L0373	NCI_CGAP_Co11	tumor	colon			Bluescript SK-
L0374	NCI_CGAP_Co2	tumor	colon			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0378	NCI_CGAP_Lu1	lung tumor	lung			Bluescript SK-
L0383	NCI_CGAP_Pr24	invasive tumor (cell line)	prostate			Bluescript SK-
L0385	NCI_CGAP_Gas1	gastric tumor	stomach			Bluescript SK-
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil			Bluescript SK-
L0393	B, Human Liver tissue					gt11
L0415	b4HB3MA Cot8- HAP-Ft					Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares 1NIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA

L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0462	WATM1					lambda gt11
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0483	Human pancreatic islet					Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215	skeletal muscle	leg muscle			Lambda ZAPII
L0508	NCI CGAP_Lu25	bronchioalveolar carcinoma	lung			pAMP1
L0515	NCI CGAP_Ov32	papillary serous carcinoma	ovary			pAMP1
L0517	NCI CGAP_Pr1					pAMP10
L0518	NCI CGAP_Pr2					pAMP10
L0519	NCI CGAP_Pr3					pAMP10
L0520	NCI CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI CGAP_Ew1	Ewing's sarcoma				pAMP10
L0523	NCI CGAP_Lip2	liposarcoma				pAMP10
L0526	NCI CGAP_Pr12	metastatic prostate bone lesion				pAMP10
L0527	NCI CGAP_Ov2	ovary				pAMP10
L0529	NCI CGAP_Pr6	prostate				pAMP10
L0533	NCI CGAP_HSC1	stem cells	bone marrow			pAMP10
L0534	Chromosome 7 Fetal Brain cDNA Library	brain	brain			pAMP10
L0535	NCI CGAP_Br5	infiltrating ductal carcinoma	breast			pAMP10
L0539	Chromosome 7 Placental cDNA Library		placenta			pAMP10
L0543	NCI CGAP_Pr9	normal prostatic epithelial cells	prostate			pAMP10
L0545	NCI CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0547	NCI CGAP_Pr16	tumor	prostate			pAMP10
L0558	NCI CGAP_Ov40	endometrioid ovarian metastasis	ovary			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0589	Stratagene fetal retina 937202					pBluescript SK-



L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234					pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0607	NCI_CGAP_Lym6	mantle cell lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0615	22 week old human fetal liver cDNA library					pBluescriptII SK(-)
L0617	Chromosome 22 exon					pBluescriptII KS+
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0627	NCI_CGAP_Co1	bulk tumor	colon			pCMV-SPORT2
L0634	NCI_CGAP_Ov8	serous adenocarcinoma	ovary			pCMV-SPORT4
L0639	NCI_CGAP_Brn52	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa tumor	colon			pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately-differentiated adenocarcinoma	colon			pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high-grade transitional cell tumors	genitourinary tract			pCMV-SPORT6

L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcino	uterus			pCMV-SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma,	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0697	Testis 1					PGEM 5zf(+)
L0698	Testis 2					PGEM 5zf(+)
L0717	Gessler Wilms tumor					pSPORT1
L0731	Soares_pregnant_uterus NbHPU		uterus			pT7T3-Pac
L0738	Human colorectal cancer					pT7T3D
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia) with a modified

						polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_ NbHH19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_s pleen_1NFLS_S1		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_ NbHL19W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_ tumor_NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_glan d_N3HPG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to 9weeks_2NbHP8to9 W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares multiple scl	multiple sclerosis				pT7T3D

	erosis_2NbHMSP	lesions				(Pharmacia) with a modified polylinker V TYPE
L0757	Soares_senescent_fi broblasts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_ Nb2HF8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic lymphotic leukemia				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0765	NCI_CGAP_Co4	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon			pT7T3D-Pac (Pharmacia)

						with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0778	Barstead pancreas HPLRB1		pancreas			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GB C_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9 W_OT_PA_P_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0786	Soares_NbHFB		whole brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker

L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker

**TABLE 5**

OMIM	Description
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Reference	
100710	Myasthenic syndrome, slow-channel congenital, 601462
103000	Hemolytic anemia due to adenylate kinase deficiency
103581	Albright hereditary osteodystrophy-2
103850	Aldolase A deficiency
106300	Ankylosing spondylitis
107250	Anterior segment mesenchymal dysgenesis
107280	Cerebrovascular disease, occlusive
107280	Alpha-1-antichymotrypsin deficiency
107400	Emphysema
107400	Emphysema-cirrhosis
107776	Colton blood group, 110450
108725	Atherosclerosis, susceptibility to
108800	Atrial septal defect, secundum type
109565	Lymphoma, B-cell
109565	Lymphoma, diffuse large cell
109690	Asthma, nocturnal, susceptibility to
109690	Obesity, susceptibility to
112261	Fibrodysplasia ossificans progressiva
114290	Campomelic dysplasia with autosomal sex reversal
114350	Leukemia, acute myeloid
114835	Monocyte carboxyesterase deficiency
116806	Colorectal cancer
120120	Epidermolysis bullosa dystrophica, dominant, 131750
120120	Epidermolysis bullosa dystrophica, recessive, 226600
120120	Epidermolysis bullosa, pretibial, 131850
120220	Bethlem myopathy, 158810
120240	Bethlem myopathy, 158810
120290	OSMED syndrome, 215150
120290	Stickler syndrome, type II, 184840
120436	Muir-Torre family cancer syndrome, 158320
120436	Turcot syndrome with glioblastoma, 276300
120436	Colorectal cancer, hereditary nonpolyposis, type 2
120700	C3 deficiency
120810	C4 deficiency
120820	C4 deficiency
120900	C5 deficiency
121050	Contractural arachnodactyly, congenital
121360	Myeloid leukemia, acute, M4Eo subtype
122500	[Transcortin deficiency]
123000	Cranio metaphyseal dysplasia
123580	Cataract, congenital, autosomal dominant
123620	Cataract, cerulean, type 2, 601547
125270	Porphyria, acute hepatic
125270	Lead poisoning, susceptibility to

126337	Myxoid liposarcoma
126650	Chloride diarrhea, congenital, Finnish type, 214700
126650	Colon cancer
128100	Dystonia-1, torsion
131195	Hereditary hemorrhagic telangiectasia-1, 187300
131400	Eosinophilia, familial
133171	[Erythrocytosis, familial], 133100
134580	Factor XIIIB deficiency
134934	Thanatophoric dysplasia, types I and II, 187600
134934	Achondroplasia, 100800
134934	Craniosynostosis, nonsyndromic
134934	Crouzon syndrome with acanthosis nigricans
134934	Hypochondroplasia, 146000
135750	Tetramelic mirror-image polydactyly
136550	Macular dystrophy, North Carolina type
136836	Fucosyltransferase-6 deficiency
137350	Amyloidosis, Finnish type, 105120
138033	Diabetes mellitus, type II
138040	Cortisol resistance
138079	Hyperinsulinism, familial, 602485
138079	MODY, type 2, 125851
138320	Hemolytic anemia due to glutathione peroxidase deficiency
139191	Growth hormone deficient dwarfism
139330	Night blindness, congenital stationary
139360	Pituitary ACTH-secreting adenoma
141750	Alpha-thalassemia/mental retardation syndrome, type 1
141800	Methemoglobinemias, alpha-
141800	Thalassemias, alpha-
141800	Erythremias, alpha-
141800	Heinz body anemias, alpha-
141850	Thalassemia, alpha-
141850	Erythrocytosis
141850	Heinz body anemia
141850	Hemoglobin H disease
141850	Hypochromic microcytic anemia
142640	Thrombophilia due to elevated HRG
142857	Pemphigoid, susceptibility to
142858	Beryllium disease, chronic, susceptibility to
142959	Hand-foot-uterus syndrome, 140000
143100	Huntington disease
143450	Trifunctional protein deficiency, type II
145001	Hyperparathyroidism-jaw tumor syndrome
145260	Pseudohypoaldosteronism, type II
145981	Hypocalciuric hypercalcemia, type II
146150	Hypomelanosis of Ito



147141	Leukemia, acute lymphoblastic
147781	Atopy, susceptibility to
148370	Keratolytic winter erythema
150250	Larsen syndrome, autosomal dominant
150270	Laryngeal adductor paralysis
150292	Epidermolysis bullosa, Herlitz junctional type, 226700
151385	Leukemia, acute myeloid
153455	Cutis laxa, recessive, type I, 219100
153880	Macular dystrophy, dominant cystoid
154276	Malignant hyperthermia susceptibility 3
154500	Treacher Collins mandibulofacial dysostosis
156845	Tietz syndrome, 103500
156845	Waardenburg syndrome, type IIA, 193510
156845	Waardenburg syndrome/ocular albinism, digenic, 103470
156850	Cataract, congenital, with microphthalmia
159000	Muscular dystrophy, limb-girdle, type 1A
160760	Cardiomyopathy, familial hypertrophic, 1, 192600
160760	Central core disease, one form
162100	Neuralgic amyotrophy with predilection for brachial plexus
164500	Spinocerebellar ataxia-7
164953	Liposarcoma
165500	Optic atrophy 1
167250	Paget disease of bone
168468	Metaphyseal chondrodysplasia, Murk Jansen type, 156400
170261	Bare lymphocyte syndrome, type I, due to TAP2 deficiency
170500	Myotonia congenita, atypical acetazolamide-responsive
170500	Paramyotonia congenita, 168300
170500	Hyperkalemic periodic paralysis
171860	Hemolytic anemia due to phosphofructokinase deficiency
172471	Glycogenosis, hepatic, autosomal
173360	Thrombophilia due to excessive plasminogen activator inhibitor
173360	Hemorrhagic diathesis due to PAI1 deficiency
176261	Jervell and Lange-Nielsen syndrome, 220400
176640	Creutzfeldt-Jakob disease, 123400
176640	Gerstmann-Straussler disease, 137440
176640	Insomnia, fatal familial
177900	Psoriasis susceptibility-1
179095	Male infertility
179450	Ragweed sensitivity
180071	Retinitis pigmentosa, autosomal recessive
180072	Night blindness, congenital stationary, type 3, 163500
180072	Retinitis pigmentosa, autosomal recessive
180090	Retinitis pigmentosa, autosomal recessive
180104	Retinitis pigmentosa-9

180297	Anemia, hemolytic, Rh-null, suppressor type, 268150
180860	Russell-Silver syndrome
181460	Schistosoma mansoni, susceptibility/resistance to
181600	Sclerotylosis
182280	Small-cell cancer of lung
182290	Smith-Magenis syndrome
182381	Renal glucosuria, 253100
182600	Spastic paraplegia-3A
182601	Spastic paraplegia-4
185000	Stomatocytosis I
186580	Arthrocutaneous granulomatosis
186880	Leukemia/lymphoma, T-cell
186960	Leukemia/lymphoma, T-cell
188070	Bleeding disorder due to defective thromboxane A2 receptor
188450	Goiter, adolescent multinodular
188450	Goiter, nonendemic, simple
188450	Hypothyroidism, hereditary congenital
189800	Preeclampsia/eclampsia
189980	Leukemia, chronic myeloid
190182	Colon cancer
190182	Colorectal cancer, familial nonpolyposis, type 6
190195	Ichthyosiform erythroderma, congenital, 242100
190195	Ichthyosis, lamellar, autosomal recessive, 242300
190685	Down syndrome
191092	Tuberous sclerosis-2
191100	Tuberous sclerosis-1
192974	Neonatal alloimmune thrombocytopenia
192974	Glycoprotein Ia deficiency
194190	Wolf-Hirschhorn syndrome
201475	VLCAD deficiency
201910	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency
203310	Ocular albinism, autosomal recessive
203740	Alpha-ketoglutarate dehydrogenase deficiency
208250	Jacobs syndrome
215700	Citrullinemia
217000	C2 deficiency
217800	Macular corneal dystrophy
218000	Andermann syndrome
218030	Apparent mineralocorticoid excess, hypertension due to
222100	Diabetes mellitus, insulin-dependent-1
222600	Atelosteogenesis II, 256050
222600	Achondrogenesis Ib, 600972
222600	Diastrophic dysplasia
222700	Lysinuric protein intolerance

223360	Dopamine-beta-hydroxylase deficiency
226450	Epidermolysis bullosa inversa, junctional
227220	[Eye color, brown]
227646	Fanconi anemia, type D
228960	[Kininogen deficiency]
233100	[Renal glucosuria]
234000	Factor XII deficiency
235200	Hemochromatosis
236100	Holoprosencephaly-1
236200	Homocystinuria, B6-responsive and nonresponsive types
236700	McKusick-Kaufman syndrome
238310	Hyperglycinemia, nonketotic, type II
238600	Chylomicronemia syndrome, familial
238600	Combined hyperlipemia, familial
238600	Hyperlipoproteinemia I
238600	Lipoprotein lipase deficiency
240300	Autoimmune polyglandular disease, type I
245200	Krabbe disease
248611	Maple syrup urine disease, type Ib
250100	Metachromatic leukodystrophy
250800	Methemoglobinemia, type I
250800	Methemoglobinemia, type II
251000	Methylmalonicaciduria, mutase deficiency type
252800	Mucopolysaccharidosis Ih
252800	Mucopolysaccharidosis Ih/s
252800	Mucopolysaccharidosis Is
256550	Sialidosis, type I
256550	Sialidosis, type II
261510	Pseudo-Zellweger syndrome
261515	Peroxisomal bifunctional enzyme deficiency
263200	Polycystic kidney disease, autosomal recessive
263700	Porphyria, congenital erythropoietic
264470	Adrenoleukodystrophy, pseudoneonatal
264600	Pseudovaginal perineoscrotal hypospadias
266300	[Hair color, red]
267750	Knobloch syndrome
268900	[Sarcosinemia]
269920	Salla disease
270200	Sjogren-Larsson syndrome
272750	GM2-gangliosidosis, AB variant
276901	Usher syndrome, type 2
278300	Xanthinuria, type I
300011	Menkes disease, 309400
300011	Occipital horn syndrome, 304150
300011	Cutis laxa, neonatal

300088	Epilepsy, female restricted, with mental retardation
300127	Mental retardation, X-linked, 60
300300	XLA and isolated growth hormone deficiency, 307200
300300	Agammaglobulinemia, type 1, X-linked
301201	Amelogenesis imperfecta-3, hypoplastic type
301500	Fabry disease
301835	Arts syndrome
303630	Alport syndrome, 301050
303630	Leiomyomatosis-nephropathy syndrome, 308940
303631	Leiomyomatosis, diffuse, with Alport syndrome
304500	Deafness, X-linked 2, perceptive congenital
304700	Mohr-Tranebjaerg syndrome
304700	Deafness, X-linked 1, progressive
304700	Jensen syndrome, 311150
305450	FG syndrome
309300	Megalocornea, X-linked
309605	Mental retardation, X-linked, syndromic-4, with congenital contractures and low fingertip arches
311850	Phosphoribosyl pyrophosphate synthetase-related gout
312080	Pelizaeus-Merzbacher disease
312080	Spastic paraplegia-2, 312920
313700	Perineal hypospadias
313700	Prostate cancer
313700	Spinal and bulbar muscular atrophy of Kennedy, 313200
313700	Breast cancer, male, with Reifenstein syndrome
313700	Androgen insensitivity, several forms
314580	Wieacker-Wolff syndrome
600044	Thrombocythemia, essential, 187950
600065	Leukocyte adhesion deficiency, 116920
600105	Retinitis pigmentosa-12, autosomal recessive
600140	Rubenstein-Taybi syndrome, 180849
600143	Epilepsy, progressive, with mental retardation
600163	Long QT syndrome-3
600184	Carnitine acetyltransferase deficiency
600202	Dyslexia, specific, 2
600211	Cleidocranial dysplasia, 119600
600243	Temperature-sensitive apoptosis
600261	Ehlers-Danlos-like syndrome
600273	Polycystic kidney disease, infantile severe, with tuberous sclerosis
600318	Diabetes mellitus, insulin-dependent, 3
600332	Rippling muscle disease-1
600635	Goiter, familial, due to TTF-1 defect
600700	Lipoma
600701	Lipoma

600759	Alzheimer disease-4
600792	Deafness, autosomal recessive 5
600807	Bronchial asthma
600808	Enuresis, nocturnal, 2
600850	Schizophrenia disorder-4
600857	Leigh syndrome
600890	Mitochondrial trifunctional protein deficiency
600890	LCHAD deficiency
600957	Persistent Mullerian duct syndrome, type I, 261550
600965	Deafness, autosomal dominant 6
600971	Deafness, autosomal recessive 6
600994	Deafness, autosomal dominant 5
600995	Nephrotic syndrome, idiopathic, steroid-resistant
601071	Deafness, autosomal recessive 9
601072	Deafness, autosomal recessive 8
601097	Neuropathy, recurrent, with pressure palsies, 162500
601097	Charcot-Marie-Tooth neuropathy-1A, 118220
601097	Dejerine-Sottas disease, PMP22 related, 145900
601145	Epilepsy, progressive myoclonic 1, 254800
601154	Cardiomyopathy, dilated, 1E
601226	Progressive external ophthalmoplegia, type 2
601238	Cerebellar ataxia, Cayman type
601267	HIV infection, susceptibility/resistance to
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601313	Polycystic kidney disease, adult type I, 173900
601369	Deafness, autosomal dominant 9
601373	HIV infection, susceptibility/resistance to
601385	Prostate cancer
601399	Platelet disorder, familial, with associated myeloid malignancy
601411	Muscular dystrophy, limb-girdle, type 2F, 601287
601472	Charcot-Marie-Tooth neuropathy-2D
601596	Charcot-Marie-Tooth neuropathy, demyelinating
601623	Angelman syndrome
601649	Blepharophimosis, epicanthus inversus, and ptosis, type 2
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601690	Platelet-activating factor acetylhydrolase deficiency
601692	Reis-Bucklers corneal dystrophy
601692	Corneal dystrophy, Avellino type
601692	Corneal dystrophy, Groenouw type I, 121900
601692	Corneal dystrophy, lattice type I, 122200
601744	Systemic lupus erythematosus, susceptibility to, 1
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601785	Carbohydrate-deficient glycoprotein syndrome, type I,

	212065
601800	[Hair color, brown]
601841	Protein C inhibitor deficiency
601846	Muscular dystrophy with rimmed vacuoles
601850	Retinitis pigmentosa-deafness syndrome
601868	Deafness, autosomal dominant 13
601889	Lymphoma, diffuse large cell
601916	Pancreatic cancer
601920	Alagille syndrome, 118450
601975	Ectodermal dysplasia/skin fragility syndrome
602086	Arrhythmogenic right ventricular dysplasia-3
602089	Hemangioma, capillary, hereditary
602116	Glioma
602117	Prader-Willi syndrome
602121	Deafness, autosomal dominant nonsyndromic sensorineural, 1, 124900
602134	Tremor, familial essential, 2
602136	Refsum disease, infantile, 266510
602136	Zellweger syndrome-1, 214100
602136	Adrenoleukodystrophy, neonatal, 202370
602216	Peutz-Jeghers syndrome, 175200
602279	Oculopharyngeal muscular dystrophy, 164300
602279	Oculopharyngeal muscular dystrophy, autosomal recessive, 257950
602280	Retinitis pigmentosa-14, 600132
602447	Coronary artery disease, susceptibility to
602460	Deafness, autosomal dominant 15, 602459
602475	Ossification of posterior longitudinal ligament of spine
602477	Febrile convulsions, familial, 2
602575	Nail-patella syndrome with open-angle glaucoma, 137750
602575	Nail-patella syndrome, 161200
602629	Dystonia-6, torsion
602666	Deafness, autosomal recessive 3, 600316
602772	Retinitis pigmentosa-24

### *Polynucleotide and Polypeptide Variants*

[0112] The present invention is also directed to variants of the digestive system associated polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A, nucleotide sequences encoding the polypeptide as defined in

column 6 of Table 1A, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1B, the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding a polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[0113] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence as defined in column 6 of Table 1A, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1B, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z.

[0114] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[0115] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature digestive system associated polypeptide; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes a biologically active fragment of a digestive system associated polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of a digestive system associated polypeptide; (e) a nucleotide sequence encoding a digestive system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (f) a nucleotide sequence encoding a mature

digestive system associated polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a biologically active fragment of a digestive system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding an antigenic fragment of a digestive system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h), above.

[0116] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A or the complementary strand thereto, nucleotide sequences encoding a polypeptide as defined in column 6 of Table 1A or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic



acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[0117] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0118] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature digestive system associated polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) the amino acid sequence of a biologically active fragment of a digestive system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of a digestive system associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

[0119] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z,

the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, the amino acid sequence as defined in column 6 of Table 1A, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[0120] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1A or 2 as the ORF (open reading frame), or any fragment specified, as described herein.

[0121] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences

are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[0122] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0123] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence

which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0124] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0125] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., an amino acid sequence identified in columns 5 or 6) or Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or an amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a

sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0126] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0127] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another

example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0128] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

[0129] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0130] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptides of the present invention without substantial loss of biological function. As an example, the authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid

residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0131] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0132] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0133] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity.

[0134] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic

acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, *inter alia*, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal digestive system or diseased digestive system tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal digestive system or diseased digestive system tissues).

[0135] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[0136] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[0137] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an anti-polypeptide of the invention antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel



diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0138] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[0139] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[0140] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, a nucleic acid sequence referred to in Table 1A (e.g., SEQ ID NO:X), a nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan

even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0141] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0142] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0143] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham et al., *Science* 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0144] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile;

replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitutions, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment or variant thereof, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0145] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[0146] A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an

amino acid sequence encoded by the complement of SEQ ID NO:X, and/or the amino acid sequence encoded by cDNA contained in Clone ID NO:Z which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[0147] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

#### *Polynucleotide and Polypeptide Fragments*

[0148] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding

a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto.

[0149] The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary strand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[0150] Moreover, representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-

4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0151] Further representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-

4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0152] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1B column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1B. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6; and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-

described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0153] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0154] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0155] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these



polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0156] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0157] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0158] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or

alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0159] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0160] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140,

141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0161] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the

residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0162] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions is preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[0163] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0164] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide

disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0165] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0166] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0167] The present application is also directed to proteins containing polypeptides

at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0168] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1B, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

[0169] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[0170] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined

from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0171] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[0172] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0173] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0174] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereto; the polypeptide sequence encoded by the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The

present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[0175] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0176] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131- 5135 (1985) further described in U.S. Patent No. 4,631,211.)

[0177] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.



Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0178] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 6 of Table 1A. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNASTar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 6 of Table 1A, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 6 of Table 1A. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0179] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient

length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0180] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0181] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or

antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0182] Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and

purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

### *Fusion Proteins*

[0183] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0184] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0185] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[0186] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-

terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[0187] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

[0188] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexahistidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton

Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984).)

[0189] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"), briefly described below, and further described herein. DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference in its entirety). In a preferred embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc., of one or more heterologous molecules encoding a heterologous polypeptide.

[0190] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

#### **Recombinant and Synthetic Production of Polypeptides of the Invention**

[0191] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0192] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

[0193] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac*, *trp*, *phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0194] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance, glutamine synthase, for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, NSO and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0195] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems

include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0196] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors is the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[0197] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of



proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0198] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0199] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., digestive system antigen coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with digestive system associated polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous digestive system associated polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous digestive system associated polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0200] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue,

in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0201] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0202] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of

the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0203] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0204] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0205] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0206] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature,

310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to; to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid,  $\gamma$ -Abu,  $\epsilon$ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, fluoro-amino acids, designer amino acids such as  $\beta$ -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0207] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0208] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0209] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of

suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine ( $^{121}\text{I}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{111}\text{In}$ ,  $^{112}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{115\text{m}}\text{In}$ ), technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ , and  $^{97}\text{Ru}$ .

[0210] In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$ , and  $^{153}\text{Sm}$ , to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is  $^{111}\text{In}$ . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is  $^{90}\text{Y}$ . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0211] As mentioned, the digestive system associated proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given digestive system associated polypeptide. Digestive system associated polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic digestive system associated polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of

flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0212] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0213] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average

molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0214] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0215] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0216] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine,

histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0217] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0218] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0219] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting



proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[0220] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0221] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[0222] The digestive system associated polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to

regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0223] Digestive system associated polynucleotides and polypeptides may be used in accordance with the present invention for a variety of applications, particularly those that make use of the chemical and biological properties of digestive system associated antigens. Among these are applications in the detection, prevention, diagnosis and/or treatment of diseases associated with the digestive system, such as e.g., cancer, tumors, biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), neoplasms (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer,

duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting); liver diseases (e.g., intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), liver failure

(hepatic encephalopathy, acute liver failure), liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)]), malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome); pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency, neoplasm (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis)); peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis). Additional applications relate to diagnosis and to treatment of disorders of cells, tissues and organisms. These aspects of the invention are discussed further below.

[0224] In a preferred embodiment, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to detect, diagnose, treat, prevent and/or prognose disorders associated with the tissue type.

[0225] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their

preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[0226] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0227] As used herein, the term heteromer refers to a multimer containing two or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[0228] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of

the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., U.S. Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0229] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found.

Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[0230] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[0231] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0232] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely

modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0233] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

### **Antibodies**

[0234] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or an epitope, of the present invention) as determined by immunoassays



well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[0235] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described *infra* and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0236] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for

different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0237] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include those shown in column 6 of Table 1A, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[0238] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic

polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

[0239] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0240] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[0241] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek et al., *Cytokine* 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0242] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[0243] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies

may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[0244] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0245] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0246] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0247] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0248] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0249] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for

generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of *Current Protocols in Immunology*, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference herein. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0250] In general, the sample containing human B cells is inoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0251] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments).

F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. For example, the antibodies of the present invention can also be generated using various phage display methods known in the art and as discussed in detail in the Examples (e.g., Example 10). In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0252] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-



34. (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0253] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0254] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0255] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923;

5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181 and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0256] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

[0257] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, J. *Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand/receptor. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[0258] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., *Hum. Gene Ther.* 5:595-601

(1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

### *Polynucleotides Encoding Antibodies*

[0259] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0260] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0261] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A<sup>+</sup> RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody

of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0262] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0263] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to

generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0264] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0265] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

#### *Methods of Producing Antibodies*

[0266] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[0267] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a

polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0268] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0269] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the

invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[0270] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In



general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0271] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0272] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0273] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-

translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0274] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0275] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp<sup>rt</sup>- or ap<sup>rt</sup>- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad.

Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0276] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0277] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the

present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

[0278] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0279] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0280] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino

acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0281] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[0282] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID-NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides

corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; Traunecker et al., *Nature* 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995)).

[0283] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

[0284] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment

regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.

[0285] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0286] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or

diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0287] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0288] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

[0289] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.



- [0290] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

#### *Immunophenotyping*

- [0291] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the genes of the present invention may be useful as cell specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell, 96:737-49 (1999)).
- [0292] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

#### *Assays For Antibody Binding*

- [0293] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such

assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0294] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyolol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[0295] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to

increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[0296] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[0297] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

[0298] Antibodies of the invention may be characterized using immunocytochemistry methods on cells (e.g., mammalian cells, such as CHO cells)

transfected with a vector enabling the expression of a digestive system antigen or with vector alone using techniques commonly known in the art. Antibodies that bind digestive system antigen transfected cells, but not vector-only transfected cells, are digestive system antigen specific.

### *Therapeutic Uses*

[0299] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0300] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the diseases, disorders, or conditions of the digestive system, including, but not limited to, biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and

peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome; deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), neoplasms (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal

incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting); liver diseases (e.g., intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), liver failure (hepatic encephalopathy, acute liver failure), liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)]), malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma,

hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome); pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency, neoplasm (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis)); peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis). Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a digestive system associated polypeptide of the invention (such as, a linear epitope (shown in Table 1A, column 6) or a conformational epitope), including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions of the digestive system described herein. The treatment and/or prevention of diseases, disorders, or conditions of the digestive system associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with these

provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0302] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0303] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0304] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

#### Gene Therapy

[0305] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy



performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0306] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0307] For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

[0308] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0309] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in*

*vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0310] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[0311] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a

retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

[0312] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0313] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0314] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0315] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection,

electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0316] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0317] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0318] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0319] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson,

Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

- [0320] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

*Demonstration of Therapeutic or Prophylactic Activity*

- [0321] The compounds or pharmaceutical compositions of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

*Therapeutic/Prophylactic Administration and Composition*

- [0322] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.
- [0323] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above;

additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0324] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0325] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0326] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein

and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

[0327] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[0328] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0329] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0330] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term

"pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0331] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry



lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0332] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0333] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0334] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

- [0335] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

*Diagnosis and Imaging*

- [0336] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

- [0337] The invention provides a diagnostic assay for diagnosing a digestive system disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0338] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0339] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. A preferred embodiment of the invention is the detection and diagnosis of a disease or disorder of the digestive system associated with aberrant expression of a digestive system antigen in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0340] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of

<sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0341] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0342] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0343] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0344] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

*Kits*

[0345] The present invention provides kits that can be used in the above methods.

In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0346] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0347] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0348] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The

diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0349] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0350] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0351] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

### Uses of the Polynucleotides

[0352] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0353] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1A, column 8 provides the chromosome location of some of the polynucleotides of the invention.

[0354] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[0355] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[0356] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see

Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0357] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0358] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1A and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0359] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999), each of which is hereby incorporated by reference in its entirety.

[0360] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Column 9 of Table 1A provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1A, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0361] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no



structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutations may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[0362] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Digestive System Disease, Including Cancer").

[0363] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[0364] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject, as further described herein. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0365] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0366] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0367] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0368] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in U.S. Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached

may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e., their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in U.S. Patents 5,858,659 and 5,856,104. The U.S. Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[0369] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254:1497 (1991); and Egholm et al., Nature 365:666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0370] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0371] The compounds of the present invention have preferred uses which include, but are not limited to, detecting cancers of digestive system tissues in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: biliary tract neoplasms, esophageal neoplasms, adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, peritoneal neoplasms, intestinal neoplasms (e.g., carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma, cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)); colonic neoplasms (e.g., colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer); liver neoplasms (e.g., angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (hepatic cysts [simple cysts, polycystic liver disease, hepatobiliary cystadenoma, choledochal cyst], mesenchymal tumors [mesenchymal hamartoma, infantile hemangioendothelioma, hemangioma, peliosis hepatis, lipomas, inflammatory pseudotumor] , epithelial tumors [bile duct epithelium (bile duct

hamartoma, bile duct adenoma), hepatocyte (adenoma, focal nodular hyperplasia, nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]) pancreatic neoplasms (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma). Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0372] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

[0373] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., *Proc. Natl. Acad. Sci.* 85:1028 (1988); Anfossi et al., *Proc. Natl. Acad. Sci.*

86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, diagnosis and/or prognosis, of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes. In preferred embodiments, the compounds and/or methods of the invention are used to treat, prevent, diagnose, and/or prognose, proliferative disorders of digestive system cells and tissues.

[0374] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[0375] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods" and Examples 16, 17 and 18).

[0376] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0377] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0378] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used

in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes..

[0379] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to, those sequences referred to in Table 1A. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[0380] Because digestive system antigens are found expressed in digestive system tissues, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In a specific embodiment, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of digestive system tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of digestive system tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, normal digestive system or diseased digestive system tissues, and/or those tissues/cells corresponding to the library source relating to a



polynucleotide sequence of the invention as disclosed in column 7 of Table 1A, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[0381] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0382] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### **Uses of the Polypeptides**

[0383] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0384] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0385] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (see, e.g., Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression

include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0386] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[0387] A digestive system antigen-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a digestive system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al.,

"Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0388] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0389] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0390] In a preferred embodiment, the invention provides a method for the specific destruction of digestive system cells (e.g., aberrant digestive system cells, digestive system neoplasm) by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs. In another preferred embodiment the invention provides a method for the specific destruction of tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0391] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha

toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0392] In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{90}\text{Y}$ . In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{111}\text{In}$ . In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope  $^{131}\text{I}$ .

[0393] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0394] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for

detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0395] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions of the digestive system such as, for example, biliary tract diseases, including, but not limited to, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), neoplasms (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small

intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting); liver diseases (e.g., intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), liver failure (hepatic encephalopathy, acute liver failure), liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases,

epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome); pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency, neoplasm (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis)); peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis). In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used

in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0396] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0397] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

#### **Diagnostic Assays**

[0398] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various digestive system related disorders in mammals, preferably humans. Such disorders include, but are not limited to, biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis,



esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), neoplasms (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis,

stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting); liver diseases (e.g., intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), liver failure (hepatic encephalopathy, acute liver failure), liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome); pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula,

insufficiency, neoplasm (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis)); peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis). In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type.

[0399] Digestive system antigens are expressed in digestive system tissues. For a number of digestive system-related disorders, substantially altered (increased or decreased) levels of digestive system antigen gene expression can be detected in digestive system tissue or other cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" digestive system antigen gene expression level, that is, the digestive system antigen expression level in digestive system tissues or bodily fluids from an individual not having the digestive system disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a digestive system system disorder, which involves measuring the expression level of the gene encoding the digestive system associated polypeptide in digestive system tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard digestive system antigens gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a digestive system disorder.

[0400] In specific embodiments, the invention provides a diagnostic method useful during diagnosis of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A, which involves measuring the expression level of the coding sequence of a polynucleotide sequence associated with this tissue/cell source as disclosed in Table 1A in the tissue/cell source or other cells or body fluid from an individual and comparing the expression level of the coding sequence with a standard expression level of the coding sequence of a polynucleotide sequence, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder of a normal or diseased tissue/cell source corresponding to

column 7 of Table 1A.

[0401] In particular, it is believed that certain tissues in mammals with cancer of cells or tissue of the digestive system express significantly enhanced or reduced levels of normal or altered digestive system antigen expression and mRNA encoding the digestive system associated polypeptide when compared to a corresponding "standard" level. Further, it is believed that enhanced or depressed levels of the digestive system associated polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) or cells or tissue from mammals with such a cancer when compared to sera from mammals of the same species not having the cancer.

[0402] For example, as disclosed herein, digestive system associated polypeptides of the invention are expressed in digestive system tissues. Accordingly, polynucleotides of the invention (e.g., polynucleotide sequences complementary to all or a portion of a digestive system antigen mRNA nucleotide sequence of SEQ ID NO:X, nucleotide sequence encoding SEQ ID NO:Y, nucleotide sequence encoding a polypeptide encoded by SEQ ID NO:X and/or a nucleotide sequence delineated by columns 8 and 9 of Table 2) and antibodies (and antibody fragments) directed against the polypeptides of the invention may be used to quantitate or qualitate concentrations of cells of the digestive system expressing digestive system antigens, preferably on their cell surfaces. These polynucleotides and antibodies additionally have diagnostic applications in detecting abnormalities in the level of digestive system antigens gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of digestive system antigens. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding digestive system sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0403] Thus, the invention provides a diagnostic method useful during diagnosis of a digestive system disorder, including cancers, which involves measuring the expression level of the gene encoding the digestive system antigen polypeptide in digestive system tissue or other cells or body fluid from an individual and comparing

the measured gene expression level with a standard digestive system antigen gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a digestive system disorder. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding digestive system sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0404] Where a diagnosis of a disorder in the digestive system, including diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed digestive system antigen gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0405] By "assaying the expression level of the gene encoding the digestive system associated polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the digestive system antigen polypeptide or the level of the mRNA encoding the digestive system antigen polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the digestive system associated polypeptide level or mRNA level in a second biological sample). Preferably, the digestive system antigen polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard digestive system antigen polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder of the digestive system. As will be appreciated in the art, once a standard digestive system antigen polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0406] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing digestive system antigen polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) which

contain cells expressing digestive system antigen polypeptides, digestive system tissue, and other tissue sources found to express the full length or fragments thereof of a digestive system antigen. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0407] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, *Anal. Biochem.* 162:156-159 (1987). Levels of mRNA encoding the digestive system antigen polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0408] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of digestive system antigen polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of digestive system antigens compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a digestive system antigen polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying digestive system antigen polypeptide levels in a biological sample can occur using any art-known method.

[0409] Assaying digestive system antigen polypeptide levels in a biological sample can occur using antibody-based techniques. For example, digestive system antigen polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., *J. Cell. Biol.* 101:976-985 (1985); Jalkanen, M., et al., *J. Cell. Biol.* 105:3087-3096 (1987)). Other antibody-based methods useful for detecting digestive system antigen polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and

the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0410] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the digestive system antigen gene (such as, for example, cells of the digestive system or digestive system cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the digestive system antigen gene.

[0411] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of digestive system antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0412] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the digestive system antigen polypeptides (Shown in Table 1A, column 6) may be used to quantitatively or qualitatively detect the presence of digestive system antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0413] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a digestive system antigen may be used to quantitatively or qualitatively detect the presence of digestive system antigen gene products or conserved variants or peptide fragments thereof. This can be

accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0414] The antibodies (or fragments thereof), and/or digestive system antigen polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of digestive system antigen gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or digestive system antigen polypeptide of the present invention. The antibody (or fragment thereof) or digestive system antigen polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the digestive system antigen gene product, or conserved variants or peptide fragments, or digestive system antigen polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0415] Immunoassays and non-immunoassays for digestive system antigen gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding digestive system antigen gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0416] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-digestive system antigen antibody or detectable digestive system antigen polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is



subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0417] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0418] The binding activity of a given lot of anti-digestive system antigen antibody or digestive system antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0419] In addition to assaying digestive system antigen polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, digestive system antigen polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, digestive system antigen polypeptide and/or anti-digestive system antigen antibodies are used to image digestive system system diseased cells, such as neoplasms. In another embodiment, digestive system antigen polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of digestive system antigen mRNA) and/or anti-digestive system antigen antibodies (e.g., antibodies directed to any one or a combination of the epitopes of digestive system antigens, antibodies directed to a conformational epitope of digestive system antigens, antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to

image diseased or neoplastic cells of the digestive system.

[0420] Antibody labels or markers for *in vivo* imaging of digestive system antigen polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of digestive system antigen polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).

[0421] Additionally, any digestive system antigen polypeptides whose presence can be detected, can be administered. For example, digestive system antigen polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such digestive system antigen polypeptides can be utilized for *in vitro* diagnostic procedures.

[0422] A digestive system antigen polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a digestive system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20

millicuries of  $^{99m}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain digestive system antigen protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0423] With respect to antibodies, one of the ways in which the anti-digestive system antigen antibody can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL.; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kigaku Shoin, Tokyo). The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0424] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect digestive system antigens through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The

Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0425] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0426] The antibody can also be detectably labeled using fluorescence emitting metals such as  $^{152}\text{Eu}$ , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0427] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[0428] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

#### **Methods for Detecting Digestive System Diseases, Including Cancer**

[0429] In general, a digestive system disease or cancer may be detected in a patient based on the presence of one or more digestive system antigen proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins and/or polynucleotides may be used as markers to indicate the presence or absence of a digestive system disease or disorder, including cancer.

Cancers that may be diagnosed, and/or prognosed using the compositions of the invention include but are not limited to, cancer of the digestive system. In addition, such proteins and/or polynucleotides may be useful for the detection of other diseases and cancers, including cancers of tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding digestive system sequence disclosed in the same row of Table 1A. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding digestive system antigen polypeptides, which is also indicative of the presence or absence of a digestive system disease or disorder, including cancer. In general, digestive system antigen polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[0430] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a digestive system disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[0431] In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the digestive system antigen polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such

assays include digestive system antigen polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[0432] The solid support may be any material known to those of skill in the art to which digestive system antigen polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0433] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

**Gene Therapy Methods**

[0434] Also encompassed by the present invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a digestive system antigen of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0435] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldgrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0436] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0437] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or

facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0438] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0439] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0440] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0441] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and



connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0442] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0443] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0444] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0445] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0446] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0447] Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y., (see, also, Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0448] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0449] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC),

dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0450] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0451] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid

fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[0452] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0453] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and International Publication No. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0454] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0455] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described

in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and  $\text{CaPO}_4$  precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0456] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

[0457] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, et al., Am. Rev. Respir. Dis. 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1991)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al., Proc. Natl. Acad. Sci. USA 76:6606 (1979)).

[0458] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively

express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0459] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0460] In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0461] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the

polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[0462] Another method of gene therapy involves operably associating heterologous control regions and endogenous digestive system antigen polynucleotide sequences (e.g., encoding a digestive system antigen polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0463] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0464] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0465] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection,

topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0466] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0467] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the digestive system antigen polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0468] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0469] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0470] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the



surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0471] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[0472] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0473] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0474] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

**Biological Activities**

[0475] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat, prevent diagnose and/or prognose the associated disease.

[0476] The digestive system antigen polynucleotides and polypeptides of the invention are predicted to have predominant expression in digestive system tissues. Thus, the digestive system antigens of the invention may be useful as therapeutic molecules. Each would be useful for diagnosis, detection, treatment and/or prevention of diseases or disorders of the digestive system, including but not limited to, biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), neoplasms (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma); stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical

hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps, colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting); liver diseases (e.g., intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C,

hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), liver failure (hepatic encephalopathy, acute liver failure), liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)]), malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome); pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency, neoplasm (adenocarcinoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis)); and/or peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis).

[0477] In a preferred embodiment, polynucleotides of the invention (e.g., a nucleic acid sequence of SEQ ID NO:X or the complement thereof; or the cDNA sequence

contained in Clone ID NO:Z, or fragments or variants thereof) and/or polypeptides of the invention (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, or the complement thereof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z and fragments or variants thereof as described herein) are useful for the diagnosis, detection, treatment, and/or prevention of diseases or disorders of the tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding digestive system sequence disclosed in the same row of Table 1A.

[0478] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0479] Particularly, the digestive system antigens may be a useful therapeutic for cancers of the digestive system. Treatment, diagnosis, detection, and/or prevention of digestive system disorders could be carried out using a digestive system antigen or soluble form of a digestive system antigen, a digestive system antigen ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of a digestive system antigen, either blocking antibodies or mutant forms, could modulate the expression of the digestive system antigen. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of a digestive system antigen.

[0480] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., normal or diseased digestive system cells) by administering polypeptides of the invention (e.g., digestive system antigen polypeptides or anti-digestive system antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., an aberrant digestive system cell or digestive system cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate

into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0481] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of aberrant digestive system cells, including, but not limited to, digestive system tumor cells) by administering polypeptides of the invention (e.g., digestive system antigen polypeptides or fragments thereof, or anti-digestive system antigen antibodies) in association with toxins or cytotoxic prodrugs.

[0482] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0483] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone,

mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0484] By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

[0485] It will be appreciated that conditions caused by a decrease in the standard or normal level of a digestive system antigen activity in an individual, particularly disorders of the digestive system, can be treated by administration of a digestive system antigen polypeptide (e.g., such as, for example, the complete digestive system antigen polypeptide, the soluble form of the extracellular domain of a digestive system antigen polypeptide, or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of digestive system antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated digestive system antigen polypeptide of the invention, or agonist thereof (e.g., an agonistic anti-digestive system antigen antibody), effective to increase the digestive system antigen activity level in such an individual.

[0486] It will also be appreciated that conditions caused by a increase in the standard or normal level of digestive system antigen activity in an individual, particularly disorders of the digestive system, can be treated by administration of digestive system antigen polypeptides (e.g., such as, for example, the complete

digestive system antigen polypeptide, the soluble form of the extracellular domain of a digestive system antigen polypeptide, or cells expressing the complete protein) or antagonist (e.g., an antagonistic digestive system antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an decreased level of digestive system antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated digestive system antigen polypeptide of the invention, or antagonist thereof (e.g., an antagonistic anti-digestive system antigen antibody), effective to decrease the digestive system antigen activity level in such an individual.

[0487] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

#### **Gastrointestinal Disorders**

[0488] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammations, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-hodgkin's lymphoma of the small intestine, small bowel lymphoma), and ulcers, such as peptic ulcers.

[0489] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess, tuberculosis).

[0490] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue,



Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

[0491] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E)), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative

hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, yolk sac tumor, carcinoid, squamous carcinoma, primary lymphoma)], peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), hepatic tuberculosis, Zellweger syndrome).

[0492] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency).

[0493] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[0494] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop

syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[0495] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g.,

congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms),

[0496] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### **Immune Activity**

[0497] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[0498] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the

polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0499] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0500] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[0501] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-

lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0502] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[0503] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0504] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0505] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0506] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation,

differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0507] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Schoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0508] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0509] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement

membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0510] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomyopathy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0511] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0512] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.



[0513] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0514] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0515] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[0516] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0517] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0518] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or

prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0519] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis; myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogeneic transplant rejection).

[0520] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis,

balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0521] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0522] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases; including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0523] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated,

detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0524] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[0525] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0526] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune

response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0527] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[0528] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0529] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0530] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0531] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and

immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0532] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

[0533] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

[0534] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0535] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

[0536] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

[0537] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0538] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0539] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first

administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0540] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0541] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0542] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0543] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0544] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce

tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0545] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

[0546] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[0547] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immunoincompetence/immunodeficiency such as observed among SCID patients.

[0548] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0549] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0550] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

[0551] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be



desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0552] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0553] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0554] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0555] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0556] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0557] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

- [0558] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.
- [0559] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.
- [0560] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).
- [0561] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.
- [0562] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0563] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0564] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0565] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0566] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0567] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[0568] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9).

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[0569] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

#### **Blood-Related Disorders**

[0570] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0571] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis,

thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0572] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0573] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells

may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0574] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0575] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadruugs. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0576] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or

diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[0577] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0578] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0579] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0580] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[0581] Leukopenia may be a generalized decrease in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an



individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0582] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited to lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

[0583] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0584] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0585] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0586] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0587] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

[0588] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0589] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

[0590] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0591] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[0592] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

**Hyperproliferative Disorders**

[0593] Digestive system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, diagnose and/or prognose hyperproliferative diseases, disorders, and/or conditions, including neoplasms.

[0594] In a specific embodiment, digestive system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions of the digestive system.

[0595] In a preferred embodiment, digestive system associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose digestive system neoplasms.

[0596] Digestive system associated polynucleotides or polypeptides, or agonists or antagonists of the invention, may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, digestive system associated polynucleotides or polypeptides, or agonists or antagonists thereof, may proliferate other cells, which can inhibit the hyperproliferative disorder.

[0597] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating, preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

[0598] Examples of hyperproliferative diseases, disorders, and/or conditions that can be treated, prevented, and/or diagnosed by digestive system associated polynucleotides or polypeptides, or agonists or antagonists thereof, include, but are not limited to neoplasms located in the: prostate, colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

[0599] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia,

Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0600] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described

above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0601] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0602] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0603] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss

in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriодigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciодigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertеbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0604] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0605] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to

diagnose and/or prognose hyperproliferative disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0606] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0607] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0608] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.



[0609] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

[0610] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis)

myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0611] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0612] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0613] One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0614] Thus, the present invention provides a method for treating cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease, disorder, and/or condition.

[0615] In a preferred embodiment, the present invention provides a method for treating cell proliferative diseases, disorders and/or conditions of the digestive system by inserting into a cell, a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease and/or disorder.

[0616] Another embodiment of the present invention provides a method of treating cell-proliferative diseases, disorders, and/or conditions in individuals comprising

administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (see, e.g., G J. Nabel, et. al., PNAS 96: 324-326 (1999), which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e., magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e., to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0617] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0618] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature

320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0619] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0620] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0621] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0622] The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described diseases, disorders, and/or conditions. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0623] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g., as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0624] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation diseases, disorders, and/or conditions as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[0625] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0626] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diseases, disorders, and/or conditions related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ .

$8M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

[0627] Moreover, digestive system antigen polypeptides of the present invention or fragments thereof, are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (see, e.g., Joseph IB, et al. *J Natl Cancer Inst*, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (see, e.g., Witte L, et al., *Cancer Metastasis Rev.* 17(2):155-61 (1998), which is hereby incorporated by reference)).

[0628] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (see, e.g., Schulze-Osthoff K, et al., *Eur J Biochem* 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, *Mutat. Res.* 400(1-2):447-55 (1998), *Med Hypotheses*.50(5):423-33 (1998), *Chem. Biol. Interact.* Apr 24;111-112:23-34 (1998), *J. Mo. Med.* 76(6):402-12 (1998), *Int. J. Tissue React.* 20(1):3-15 (1998), which are all hereby incorporated by reference).

[0629] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues.

Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants

[0630] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or anti-digestive system antigen polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Digestive system antigen polypeptides or anti-digestive system antigen polypeptide antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0631] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

#### **Urinary System Disorders**

[0632] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the urinary system, including but not limited to disorders of the renal system, bladder, ureters, and urethra. Renal disorders include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0633] Kidney failure diseases include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, and end-stage renal disease. Inflammatory diseases of the kidney include acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis.

[0634] Blood vessel disorders of the kidneys include, but are not limited to, kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis. Kidney disorders resulting from urinary tract problems include, but are not limited to, pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.

[0635] Metabolic and congenital disorders of the kidneys include, but are not limited to, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, vitamin D-resistant rickets, Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy. Kidney disorders resulting from an autoimmune response include, but are not limited to, systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis.

[0636] Sclerotic or necrotic disorders of the kidney include, but are not limited to, glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis. Kidneys may also develop carcinomas, including, but not limited to, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, squamous cell cancer, and Wilm's tumor.



[0637] Kidney disorders may also result in electrolyte imbalances, including, but not limited to, nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia.

[0638] Bladder disorders include, but are not limited to, benign prostatic hyperplasia (BPH), interstitial cystitis (IC), prostatitis, proteinuria, urinary tract infections, urinary incontinence, urinary retention. Disorders of the ureters and urethra include, but are not limited to, acute or chronic unilateral obstructive uropathy. The bladder, ureters, and urethra may also develop carcinomas, including, but not limited to, superficial bladder cancer, invasive bladder cancer, carcinoma of the ureter, and urethra cancers.

[0639] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

### **Cardiovascular Disorders**

[0640] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0641] Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot,

transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, total anomalous pulmonary venous connection, hypoplastic left heart syndrome, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, atrioventricular canal defect, trilogy of Fallot, ventricular heart septal defects.

[0642] Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, sudden cardiac death, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, diastolic dysfunction, enlarged heart, heart block, J-curve phenomenon, rheumatic heart disease, Marfan syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0643] Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0644] Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, tricuspid valve stenosis, and bicuspid aortic valve.

[0645] Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, Barth syndrome, myocardial reperfusion injury, and myocarditis.

[0646] Myocardial ischemias include coronary disease, such as angina pectoris, Prinzmetal's angina, unstable angina, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0647] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension (shock), ischemia, peripheral vascular diseases, phlebitis, superficial phlebitis, pulmonary veno-occlusive disease, chronic obstructive pulmonary disease, Buerger's disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, deep vein thrombosis, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0648] Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0649] Arterial occlusive diseases include arteriosclerosis, arteriolosclerosis, atherosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0650] Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and

thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0651] Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, deep vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0652] Ischemia includes cerebral ischemia, ischemic colitis, silent ischemia, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0653] Cardiovascular diseases can also occur due to electrolyte imbalances that include, but are not limited to hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia. Neoplasm and/or cancers of the cardiovascular system include, but are not limited to, myxomas, fibromas, and rhabdomyomas.

[0654] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

**Respiratory Disorders**

[0655] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0656] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis))), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0657] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia spp.*), opportunistic infection pneumonia, nosocomial pneumonia, chemical

pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

#### **Anti-Angiogenesis Activity**

[0658] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and

Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

[0659] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administration to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0660] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate

mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0661] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[0662] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[0663] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0664] Moreover, ocular disorders associated with neovascularization which can



be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

[0665] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue, which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0666] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer, which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in

corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0667] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation, the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form, injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[0668] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[0669] Within particularly preferred embodiments of the invention, proliferative

diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0670] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

[0671] Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0672] Moreover, disorders and/or states, which can be treated, prevented, diagnosed and/or prognosed with the polynucleotides, polypeptides, agonists and/or antagonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence

such as cat scratch disease (*Rochela minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

[0673] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0674] Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0675] Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes, which have been coated with anti-angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0676] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or

otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0677] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or antagonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0678] The polynucleotides, polypeptides, agonists and/or antagonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0679] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0680] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0681] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable

tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0682] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., *Cancer Res.* 51:22-26 (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs,  $\alpha$ -hydroxyproline, d,L-3,4-dehydroproline, Thiaproline,  $\alpha,\alpha$ -dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326 (1992)); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480 (1992)); Cyclodextrin Tetradesulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557 (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446 (1987)); anticollagenase-serum;  $\alpha$ 2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664 (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., *Agents Actions* 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

### **Musculoskeletal System Disorders**

[0683] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose

disorders of the musculoskeletal system, including but not limited to, disorders of the bone, joints, ligaments, tendons, bursa, muscle, and/or neoplasms and cancers associated with musculoskeletal tissue.

[0684] Diseases or disorders of the bone include, but are not limited to, Albers-Schönberg disease, bowlegs, heel spurs, Köhler's bone disease, knock-knees, Legg-Calvé-Perthes disease, Marfan's syndrome, mucopolysaccharidoses, Osgood-Schlatter disease, osteochondroses, osteochondrodysplasia, osteomyelitis, osteopetroses, osteoporosis (postmenopausal, senile, and juvenile), Paget's disease, Scheuermann's disease, scoliosis, Sever's disease, and patellofemoral stress syndrome.

[0685] Joint diseases or disorders include, but are not limited to, ankylosing spondylitis, Behçet's syndrome, CREST syndrome, Ehlers-Danlos syndrome, infectious arthritis, discoid lupus erythematosus, systemic lupus erythematosus, Lyme disease, osteoarthritis, psoriatic arthritis, relapsing polychondrites, Reiter's syndrome, rheumatoid arthritis (adult and juvenile), scleroderma, and Still's disease.

[0686] Diseases or disorders affecting ligaments, tendons, or bursa include, but are not limited to, ankle sprain, bursitis, posterior Achilles tendon bursitis (Haglund's deformity), anterior Achilles tendon bursitis (Albert's disease), tendinitis, tenosynovitis, popliteus tendinitis, Achilles tendinitis, medial or lateral epicondylitis, rotator cuff tendinitis, spasmodic torticollis, and fibromyalgia syndrome.

[0687] Muscle diseases or disorders include, but are not limited to, Becker's muscular dystrophy, Duchenne's muscular dystrophy, Landouzy-Dejerine muscular dystrophy, Leyden-Möbius muscular dystrophy, Erb's muscular dystrophy, Charcot's joints, dermatomyositis, gout, pseudogout, glycogen storage diseases, Pompe's disease, mitochondrial myopathy, periodic paralysis, polymyalgia rheumatica, polymyositis, Steinert's disease, Thomsen's disease, anterolateral and posteromedial shin splints, posterior femoral muscle strain, and fibromyositis.

[0688] Musculoskeletal tissue may also develop cancers and/or neoplasms that include, but are not limited to, osteochondroma, benign chondroma, chondroblastoma, chondromyxoid fibroma, osteoid osteoma, giant cell tumor, multiple myeloma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's tumor, and malignant lymphoma of bone.

**Neural Activity and Neurological Diseases**

[0689] The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy,



Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[0690] In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[0691] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[0692] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[0693] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way

of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[0694] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[0695] Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists

or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[0696] Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[0697] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[0698] Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[0699] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[0700] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral

encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[0701] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[0702] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uveomeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as

Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[0703] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerosis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chiari Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[0704] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie

Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies,

autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[0705] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

### **Endocrine Disorders**

[0706] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.



[0707] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0708] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor; post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0709] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0710] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0711] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[0712] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose endocrine system disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, 7 (Tissue Distribution Library Code).

### **Reproductive System Disorders**

[0713] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0714] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including, but not limited to, testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas,

choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[0715] Reproductive system disorders also include, but are not limited to, disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0716] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including, but not limited to, inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis, giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[0717] Moreover, diseases and/or disorders of the vas deferens include, but are not limited to, vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including but not limited to, hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0718] Other disorders and/or diseases of the male reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[0719] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including, but not limited to, bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[0720] Disorders and/or diseases of the uterus that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

[0721] Ovarian diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to,

anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0722] Cervical diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0723] Additionally, diseases and/or disorders of the reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus erythematosus, rheumatoid

arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

[0724] Complications associated with labor and parturition that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[0725] Further, diseases and/or disorders of the postdelivery period, that may be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[0726] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, but are not limited to, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

#### **Developmental and Inherited Disorders**

[0727] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases associated with mixed fetal tissues, including, but not limited to, developmental and inherited disorders or defects of the nervous system, musculoskeletal system, excretory system, cardiovascular system, hematopoietic system, gastrointestinal system, reproductive system, and respiratory system. Compositions of the present invention may also be used to treat, prevent, diagnose, and/or prognose developmental and inherited disorders or defects associated with, but not limited to, skin, hair, visual, and auditory tissues, metabolism. Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases associated with,

but not limited to, chromosomal or genetic abnormalities and hyperproliferation or neoplasia.

[0728] Disorders or defects of the nervous system associated with developmental or inherited abnormalities that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, adrenoleukodystrophy, agenesis of corpus callosum, Alexander disease, anencephaly, Angelman syndrome, Arnold-Chiari deformity, Batten disease, Canavan disease, cephalic disorders, Charcot-Marie-Tooth disease, encephalocele, Friedreich's ataxia, Gaucher's disease, Gorlin syndrome, Hallervorden-Spatz disease, hereditary spastic paraplegia, Huntington disease, hydranencephaly, hydrocephalus, Joubert syndrome, Lesch-Nyhan syndrome, leukodystrophy, Menkes disease, microcephaly, Niemann-Pick Type C1, neurofibromatosis, porencephaly, progeria, proteus syndrome, Refsum disease, spina bifida, Sturge-Weber syndrome, Tay-Sachs disease, tuberous sclerosis, and von Hippel-Lindau disease.

[0729] Developmental and inherited disorders resulting in disorders or defects of the musculoskeletal system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, achondroplasia, atlanto-occipital fusion, arthrogryposis multiplex congenita, autosomal recessive muscular dystrophy, Becker's muscular dystrophy, cerebral palsy, choanal atresia, cleft lip, cleft palate, clubfoot, congenital amputation, congenital dislocation of the hip, congenital torticollis, congenital scoliosis, dopa-responsive dystonia, Duchenne muscular dystrophy, early-onset generalized dystonia, femoral torsion, Gorlin syndrome, hypophosphatasia, Klippel-Feil syndrome, knee dislocation, myoclonic dystonia, myotonic dystrophy, nail-patella syndrome, osteogenesis imperfecta, paroxysmal dystonia, progeria, prune-belly syndrome, rapid-onset dystonia parkinsonism, scoliosis, syndactyly, Treacher Collins' syndrome, velocardiofacial syndrome, and X-linked dystonia-parkinsonism.

[0730] Developmental or hereditary disorders or defects of the excretory system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Alport's syndrome, Bartter's syndrome, bladder diverticula, bladder exstrophy, cystinuria, epispadias, Fanconi's syndrome, Hartnup disease, horseshoe kidney, hypospadias, kidney agenesis, kidney ectopia,

kidney malrotation, Liddle's syndrome, medullary cystic disease, medullary sponge, multicystic kidney, kidney polycystic kidney disease, nail-patella syndrome, Potter's syndrome, urinary tract flow obstruction, vitamin D-resistant rickets, and Wilm's tumor.

[0731] Cardiovascular disorders or defects of developmental or hereditary origin that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, aortic valve stenosis, atrial septal defects, arterioventricular (A-V) canal defect, bicuspid aortic valve, coarctation of the aorta, dextrocardia, Ebstein's anomaly, Eisenmenger's complex, hypoplastic left heart syndrome, Marfan syndrome, patent ductus arteriosus, progeria, pulmonary atresia, pulmonary valve stenosis, subaortic stenosis, tetralogy of fallot, total anomalous pulmonary venous (P-V) connection, transposition of the great arteries, tricuspid atresia, truncus arteriosus, ventricular septal defects. Developmental or inherited disorders resulting in disorders involving the hematopoietic system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Bernard-Soulier syndrome, Chédiak-Higashi syndrome, hemophilia, Hermansky-Pudlak syndrome, sickle cell anemia, storage pool disease, thromboxane A2 dysfunction, thrombasthenia, and von Willebrand's disease.

[0732] The compositions of the invention may also be used to diagnose, treat, and/or prevent developmental and inherited disorders resulting in disorders or defects of the gastrointestinal system, including, but not limited to, anal atresia, biliary atresia, esophageal atresia, diaphragmatic hernia, Hirschsprung's disease, Meckel's diverticulum, oligohydramnios, omphalocele, polyhydramnios, porphyria, situs inversus viscerum. Developmental or inherited disorders resulting in metabolic disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, alpha-1 antitrypsin deficiency, cystic fibrosis, hemochromatosis, lysosomal storage disease, phenylketonuria, Wilson's disease, and Zellweger syndrome.

[0733] Disorders of the reproductive system that are developmentally or hereditary related that may also be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, androgen insensitivity syndrome, ambiguous genitalia, autosomal sex reversal, congenital adrenal hyperplasia,



gonadoblastoma, ovarian germ cell cancer, pseudohermaphroditism, true hermaphroditism, undescended testis, XX male syndrome, and XY female type gonadal dysgenesis. The compositions of the invention may also be used to diagnose, treat, and/or prevent developmental or inherited respiratory defects including, but not limited to, askin tumor, azygos lobe, congenital diaphragmatic hernia, congenital lobar emphysema, cystic adenomatoid malformation, lobar emphysema, hyaline membrane disease, and pectus excavatum.

[0734] Developmental or inherited disorders may also result from chromosomal or genetic aberration that may be diagnosed, treated, and/or prevented with the compositions of the invention including, but not limited to, 4p- syndrome, cri du chat syndrome, Digeorge syndrome, Down's syndrome, Edward's syndrome, fragile X syndrome, Klinefelter's syndrome, Patau's syndrome, Prader-Willi syndrome, progeria, Turner's syndrome, triple X syndrome, and XYY syndrome. Other developmental disorders that can be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, fetal alcohol syndrome, and can be caused by environmental factors surrounding the developing fetus.

[0735] The compositions of the invention may further be able to be used to diagnose, treat, and/or prevent errors in development or a genetic disposition that may result in hyperproliferative disorders or neoplasms, including, but not limited to, acute childhood lymphoblastic leukemia, askin tumor, Beckwith-Wiedemann syndrome, childhood acute myeloid leukemia, childhood brain stem glioma, childhood cerebellar astrocytoma, childhood extracranial germ cell tumors childhood (primary), gonadoblastoma, hepatocellular cancer, childhood Hodgkin's disease, childhood Hodgkin's lymphoma, childhood hypothalamic and visual pathway glioma, childhood (primary) liver cancer, childhood lymphoblastic leukemia, childhood medulloblastoma, childhood non-Hodgkin's lymphoma, childhood pineal and supratentorial primitive neuroectodermal tumors, childhood primary liver cancer, childhood rhabdomyosarcoma, childhood soft tissue sarcoma, Gorlin syndrome, familial multiple endocrine neoplasia type I, neuroblastoma, ovarian germ cell cancer, pheochromocytoma, retinoblastoma, and Wilm's tumor.

[0736] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous

injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### **Diseases at the Cellular Level**

[0737] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0738] In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those [listed above] involving digestive system tissues.

[0739] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including

myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0740] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

**Wound Healing and Epithelial Cell Proliferation**

[0741] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss.

[0742] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentopal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0743] It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[0744] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[0745] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases, which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the

mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[0746] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dislasia, in premature infants.

[0747] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0748] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so

as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

### **Infectious Diseases**

[0749] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[0750] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic

fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

[0751] Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Nocardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria meningitidis, Pasteurellaceae Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease,



respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

[0752] Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

[0753] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

**Regeneration**

[0754] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[0755] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[0756] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[0757] Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic

lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

### **Chemotaxis**

[0758] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0759] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[0760] It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

[0761] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

[0762] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0763] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[0764] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[0765] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[0766] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[0767] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides,

for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[0768] Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0769] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0770] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and

corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[0771] Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0772] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$  thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[0773] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[0774] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[0775] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

#### **Targeted Delivery**

[0776] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[0777] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one

embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0778] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[0779] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

### **Drug Screening**

[0780] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules



which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

[0781] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[0782] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[0783] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned

drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0784] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### Antisense And Ribozyme (Antagonists)

[0785] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA Clone ID NO:Z identified for example, in Table 1A. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., *Neurochem.* 56:560 (1991). *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., *Neurochem.* 56:560 (1991); *Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression*, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

[0786] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed *in vitro* by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame

is flanked by an EcoR1 site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[0787] For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

[0788] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

[0789] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A

sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[0790] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[0791] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell

membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[0792] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[0793] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[0794] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[0795] In yet another embodiment, the antisense oligonucleotide is an  $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

[0796] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[0797] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[0798] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0799] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express *in vivo*. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[0800] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[0801] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

[0802] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[0803] The antagonist/agonist may also be employed to treat the diseases described herein.

[0804] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

**Binding Peptides and Other Molecules**

[0805] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind digestive system antigen polypeptides, and the digestive system antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the digestive system antigen polypeptides. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0806] This method comprises the steps of: contacting digestive system antigen polypeptides or digestive system antigen-like polypeptides with a plurality of molecules; and identifying a molecule that binds the digestive system antigen polypeptides or digestive system antigen-like polypeptides.

[0807] The step of contacting the digestive system antigen polypeptides or digestive system antigen-like polypeptides with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the digestive system antigen polypeptides or digestive system antigen-like polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized digestive system antigen polypeptides or digestive system antigen-like polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized digestive system antigen polypeptides or digestive system antigen-like polypeptides. The molecules having a selective affinity for the digestive system antigen polypeptides or digestive system antigen-like polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the digestive system antigen polypeptides or digestive system antigen-like polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[0808] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant



phage). Individual isolates can then be "probed" by the digestive system antigen polypeptides or digestive system antigen-like polypeptides, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the digestive system antigen polypeptides or digestive system antigen-like polypeptides and the individual clone. Prior to contacting the digestive system antigen polypeptides or digestive system antigen-like polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for digestive system antigen polypeptides or digestive system antigen-like polypeptides. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the digestive system antigen polypeptides or digestive system antigen-like polypeptides can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[0809] In certain situations, it may be desirable to wash away any unbound digestive system antigen polypeptides or digestive system antigen-like polypeptides, or alternatively, unbound polypeptides, from a mixture of the digestive system antigen polypeptides or digestive system antigen-like polypeptides and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the digestive system antigen polypeptides or digestive system antigen-like polypeptides or the plurality of polypeptides is bound to a solid support.

[0810] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind

digestive system antigen polypeptides. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710; Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

[0811] Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718; Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[0812] *In vitro* translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

[0813] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

[0814] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of

various libraries.

[0815] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[0816] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0817] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

[0818] In a specific embodiment, screening to identify a molecule that binds digestive system antigen polypeptides can be carried out by contacting the library members with a digestive system antigen polypeptides or digestive system antigen-like polypeptides immobilized on a solid phase and harvesting those library members that bind to the digestive system antigen polypeptides or digestive system antigen-like polypeptides. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes

et al., 1992, BioTechniques 13:422-427; International Publication No. WO 94/18318; and in references cited herein.

[0819] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to digestive system antigen polypeptides or digestive system antigen-like polypeptides.

[0820] Where the digestive system antigen binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[0821] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[0822] As mentioned above, in the case of a digestive system antigen binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a digestive system antigen binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[0823] The selected digestive system antigen binding polypeptide can be obtained by chemical synthesis or recombinant expression.

**Other Activities**

[0824] A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[0825] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[0826] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[0827] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[0828] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[0829] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for

supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0830] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[0831] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0832] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0833] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[0834] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

#### **Other Preferred Embodiments**

- [0835] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.
- [0836] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in column 4, "ORF (From-To)", in Table 1A.
- [0837] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in columns 8 and 9, "NT From" and "NT To" respectively, in Table 2.
- [0838] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.
- [0839] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.
- [0840] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in column 4, "ORF (From-To)", in Table 1A.
- [0841] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in columns 8 and 9, "NT From" and "NT To", respectively, in Table 2.

[0842] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.

[0843] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

[0844] Also preferred is a composition of matter comprising a DNA molecule which comprises the cDNA contained in Clone ID NO:Z.

[0845] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides of the cDNA sequence contained in Clone ID NO:Z.

[0846] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA contained in Clone ID NO:Z.

[0847] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in Clone ID NO:Z.

[0848] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in Clone ID NO:Z.

[0849] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA contained in Clone ID NO:Z.



[0850] A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in Clone ID NO:Z; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

[0851] Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[0852] A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of the cDNA contained in Clone ID NO:Z.

[0853] The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[0854] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto; or the cDNA contained in Clone ID NO:Z which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of cDNA contained in Clone ID NO:Z.

[0855] The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[0856] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in Clone ID NO:Z. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[0857] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000, or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected

from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA "Clone ID" in Table 1A.

[0858] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in Clone ID NO:Z.

[0859] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in Clone ID NO:Z.

[0860] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in Clone ID NO:Z.

[0861] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in Clone ID NO:Z.

[0862] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by contained in Clone ID NO:Z

[0863] Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded

by cDNA contained in Clone ID NO:Z; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or the polypeptide sequence of SEQ ID NO:Y.

[0864] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0865] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA contained in Clone ID NO:Z.

[0866] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0867] Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0868] Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of

said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[0869] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0870] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

[0871] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0872] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

[0873] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1A or Table 2 encoding a polypeptide, which method comprises a

step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0874] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

[0875] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0876] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

[0877] Also preferred is a polypeptide molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[0878] Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

[0879] Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in Clone ID NO:Z. The isolated polypeptide produced by this method is also preferred.

[0880] Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

[0881] Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

[0882] Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., tumors, leukemias or lymphomas), which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

[0883] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

**TABLE 6**

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081



### *Examples*

#### *Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

[0884] Each Clone ID NO:Z is contained in a plasmid. Table 7 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 7 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSPORT 2.0	pCMVSPORT 2.0
pCMVSPORT 3.0	pCMVSPORT 3.0
pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

[0885] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which

are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

[0886] Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the vector sequences identified for the particular clone in Table 7, as well as the corresponding plasmid vector sequences designated above.

[0887] The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Tables 1A, 2, 6 and 7 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each Clone ID NO:Z.

**TABLE 7**

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lamda ZAP II	LP01

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A, re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPF	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE	Human Endometrial Tumor	Uni-ZAP XR	LP03

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HETF HETG HETH HETI			
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPC HHPD HHPE HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUV C HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE HTLF	Human adult testis, large inserts	Uni-ZAP XR	LP03
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HNFA HNFH HNFC HNFD HNFE HNEF HNEG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re- excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HL-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re- excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE HSQF HSQG	Stromal cell TF274	Uni-ZAP XR	LP03
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE	Smooth muscle, control	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSLF HSLG			
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex,epileptic;re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced,re-exc	pBS	LP03
HFCA HFCE HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPC	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNB HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalamus,Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HNHE HNHF HNHG HNHH HNHI HNHI			
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNF $\alpha$ and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAL HMAD HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF- $\alpha$	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSPORT 1	LP06
HOFM HOFN HOFQ	H. Ovarian Tumor, II, OV5232	pCMVSPORT 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSPORT 2.0	LP07
HCGL	CD34+cells, II	pCMVSPORT 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSPORT 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSPORT 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSPORT 2.0	LP07

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSPORT 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSPORT2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSPORT2.0	LP07
HNDA	Nasal polyps	pCMVSPORT2.0	LP07
HDRA	H. Primary Dendritic Cells, lib 3	pCMVSPORT2.0	LP07
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSPORT2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSPORT3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSPORT3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSPORT3.0	LP08
HNTA	NTERA2, control	pCMVSPORT3.0	LP08
HDP A HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSPORT3.0	LP08
HDPM HDPN HDPO HDPP	Primary Dendritic cells, frac 2	pCMVSPORT3.0	LP08
HMUA HMUB HMUC	Myeloid Progenitor Cell Line	pCMVSPORT3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSPORT3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSPORT3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSPORT3.0	LP08
HJMA HJMB	Human endometrial stromal cells- treated with progesterone	pCMVSPORT3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells- treated with estradiol	pCMVSPORT3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSPORT3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSPORT3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSPORT3.0	LP08
HMTM	PCR, pBMC I/C treated	PCR II	LP09
HMJA	H. Meningioma, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFC	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD, HADE HADG HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library, II	pSport 1	LP10
HMMA	Spleen metastatic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10



<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells, CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac 2	pSport 1	LP10
HLDX	Human Liver, normal, CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells, untreated	pSport1	LP10
HUMA	Human Dermal Endothelial cells, treated	pSport1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate, BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH, Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFII	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Mesangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFY HFIZ	Synovial Fibroblasts (IL1/TNF), sub	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSPORT 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSPORT 1	LP012
HBBA HBBB	Human Brain	pCMVSPORT 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSPORT 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSPORT 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSPORT 2.0	LP012
HAMF HAMG	KMH2	pCMVSPORT 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSPORT 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSPORT 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSPORT 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSPORT 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSPORT 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSPORT 3.0	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSPORT 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSPORT 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSPORT 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSPORT 3.0	LP012
HWJA	Healing Abdomen Wound;21&29 days	pCMVSPORT 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meningima, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport1	LP012
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastatic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDLA	Pericardium	pSport1	LP012
HBZA	Prostate,BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKF	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HL1S	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFC A HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTHE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUV C HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPR HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCB HMCH HMCJ HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs);re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood);re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheimer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland, normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015
HHAM	Hypothalamus, Alzheimer's	pCMVSPORT 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethosone Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020

<b>Libraries owned by Catalog</b>	<b>Catalog Description</b>	<b>Vector</b>	<b>ATCC Deposit</b>
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPB, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	pSPORT1	LP022
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA,HUJB,HUJC,HUJD,HUJE	B-Cells	pCMVSPORT 3.0	LP022
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLN	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA,HUUB,HUUC,HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA,HWWB,HWWC,HWWD,HWWE,HWWF,HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSPORT 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCQ HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBU HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal-cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCA HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

[0888] Two nonlimiting examples are provided below for isolating a particular clone from the deposited sample of plasmid cDNAs cited for that clone in Table 7. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

[0889] Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ - $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

[0890] Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu\text{l}$  of reaction mixture with 0.5  $\mu\text{g}$  of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20  $\mu\text{M}$  each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with

expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[0891] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

[0892] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[0893] This above method starts with total RNA isolated from the desired source, although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[0894] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.



***Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide***

[0895] A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X according to the method described in Example 1. (See also, Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edn., (1989), Cold Spring Harbor Laboratory Press).

***Example 3: Tissue specific expression analysis***

[0896] The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue and/or disease specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs and assembled contigs which show tissue specific expression are selected.

[0897] The original clone from which the specific EST sequence was generated, or in the case of an assembled contig, the clone from which the 5' most EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured and then transferred in 96 or 384 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

[0898] Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed (e.g., colon, colon cancer, pancreas, pancreatic cancer, liver, liver cancer, stomach, stomach cancer, large intestine, large intestine, small intestine, small intestine, etc.). The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with

the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

[0899] Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified.

#### ***Example 4: Chromosomal Mapping of the Polynucleotides***

[0900] An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions are analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

#### ***Example 5: Bacterial Expression of a Polypeptide***

[0901] A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a

ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[0902] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the *E. coli* strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[0903] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[0904] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[0905] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[0906] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-

NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

[0907] In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide of the present invention. This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

[0908] DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[0909] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

***Example 6: Purification of a Polypeptide from an Inclusion Body***

[0910] The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

[0911] Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

[0912] The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

[0913] The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

[0914] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

[0915] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH

6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[0916] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

[0917] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

### ***Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System***

[0918] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal.

of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

[0919] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

[0920] Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

[0921] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0922] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

[0923] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[0924] Five  $\mu\text{g}$  of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu\text{g}$  of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu\text{g}$  of BaculoGold™ virus DNA and 5  $\mu\text{g}$  of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu\text{l}$  of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu\text{l}$  Lipofectin plus 90  $\mu\text{l}$  Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

[0925] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200  $\mu\text{l}$  of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

[0926] To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5  $\mu\text{Ci}$  of  $^{35}\text{S}$ -methionine and 5  $\mu\text{Ci}$   $^{35}\text{S}$ -cysteine (available from Amersham) are added. The cells



are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

[0927] Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

### *Example 8: Expression of a Polypeptide in Mammalian Cells*

[0928] The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[0929] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[0930] Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

[0931] The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[0932] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[0933] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[0934] A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[0935] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment

then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0936] The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[0937] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

### ***Example 9: Protein Fusions***

[0938] The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A. 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time *in vivo*. Nuclear localization signals

fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

[0939] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

[0940] For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

[0941] If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

[0942] Human IgG Fc region:

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GGGATCCGGAGCCCAAATCTTCTGACAAAACACACATGCCCAACCGTGC
CCAGCACCTGAATTTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTACATGCGTGGTG
GTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC
AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGG
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CTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAAC  
 CCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC  
 AGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTC  
 AGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAG  
 TGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGT  
 GCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAA  
 GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGG  
 CTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT  
 GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO: 1)

### *Example 10: Production of an Antibody from a Polypeptide*

#### *Hybridoma Technology*

[0943] The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[0944] Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

[0945] The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

[0946] Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

[0947] For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

*Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention  
From A Library Of scFvs*

[0948] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

[0949] *Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately  $10^9$  *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU,  $2 \times 10^8$  TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in International Application No. WO 92/01047.

[0950] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37°C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately  $10^{13}$  transducing units/ml (ampicillin-resistant clones).

[0951] *Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times

in PBS. Approximately  $10^{13}$  TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

[0952] *Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Application No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

***Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide***

[0953] RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in



SEQ ID NO:X; and/or the nucleotide sequence of the cDNA contained in Clone ID NO:Z. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

[0954] PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase (Epicentre Technologies). The intron-exon boundaries of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing.

[0955] PCR products are cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

[0956] Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

[0957] Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

***Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample***

[0958] A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

[0959] For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

[0960] The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

[0961] Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

[0962] Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

### *Example 13: Formulations*

[0963] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By "Therapeutic" is meant polynucleotides or polypeptides of the invention (including fragments, analogs, derivatives and variants thereof), agonists or antagonists thereof, and/or antibodies thereto (including fragments thereof), in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

[0964] The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[0965] As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[0966] Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include

intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0967] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0968] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

[0969] Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

[0970] Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small

(about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

[0971] In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

[0972] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0973] For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

[0974] Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[0975] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its

derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[0976] The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[0977] Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0978] Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

[0979] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

[0980] The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be

administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella); polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0981] The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0982] In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha), also

known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0983] In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.



[0984] In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[0985] In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[0986] In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[0987] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[0988] In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0989] In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin

preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0990] In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0991] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0992] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0993] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium

metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0994] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0995] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26 (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480 (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664 (1987)); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-

carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

[0996] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dextrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlitin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[0997] Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KGaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that

act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[0098] In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[0099] In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[01000] In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[01001] In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the compositions of the invention include, but are not limited to,

antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[01002] In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

[01003] In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[01004] In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent

Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., *Growth Factors*, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[01005] In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

[01006] In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[01007] In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

***Example 14: Method of Treating Decreased Levels of the Polypeptide***



[01008] The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

[01009] For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

### ***Example 15: Method of Treating Increased Levels of the Polypeptide***

[01010] The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

[01011] In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

[01012] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

***Example 16: Method of Treatment Using Gene Therapy-Ex Vivo***

[01013] One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

[01014] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[01015] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[01016] The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[01017] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with

10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

[01018] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

[01019] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

### ***Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention***

[01020] Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

[01021] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

[01022] The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel, then purified by phenol extraction and ethanol precipitation.

[01023] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[01024] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[01025] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining

cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM  $\text{Na}_2\text{HPO}_4$ , 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

[01026] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[01027] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120  $\mu\text{g/ml}$ . 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960  $\mu\text{F}$  and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[01028] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following

day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[01029] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

***Example 18: Method of Treatment Using Gene Therapy - In Vivo***

[01030] Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

[01031] The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[01032] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in

Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

[01033] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[01034] The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[01035] For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the

tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as; inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[01036] The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[01037] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[01038] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.



### *Example 19: Transgenic Animals*

[01039] The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

[01040] Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

[01041] Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campbell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

[01042] The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but

not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

[01043] Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

[01044] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate

lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

[01045] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

### ***Example 20: Knock-Out Animals***

[01046] Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (See e.g., Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety.) For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely

adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

[01047] In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

[01048] Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[01049] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an

exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

[01050] Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

***Example 21: Assays Detecting Stimulation or Inhibition of B cell  
Proliferation and Differentiation***

[01051] Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

[01052] One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

[01053] *In vitro* Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death

in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

[01054] Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$  M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with  $^3$ H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

[01055] *In Vivo* Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

[01056] Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

[01057] Likewise, a predicted consequence of increased mature B-cell representation *in vivo* is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

[01058] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 22: T Cell Proliferation Assay***

[01059] A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of <sup>3</sup>H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10<sup>4</sup>/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of <sup>3</sup>H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of <sup>3</sup>H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which

does not induce proliferation of T cells is used as the negative control for the effects of agonists or antagonists of the invention.

[01060] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 23: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells***

[01061] Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

[01062] FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[01063] Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune



responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ( $10^6/\text{ml}$ ) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

[01064] Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increased expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

[01065] FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[01066] Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red

Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

[01067]     Monocyte Survival Assay.     Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated processes (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a final concentration of 5 µg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

[01068]     Effect on cytokine release.     An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in the presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

[01069]     Oxidative burst.     Purified monocytes are plated in 96-w plate at  $2 \times 10^5$  cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10%

FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H<sub>2</sub>O<sub>2</sub> produced by the macrophages, a standard curve of a H<sub>2</sub>O<sub>2</sub> solution of known molarity is performed for each experiment.

[01070] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

#### ***Example 24: Biological Effects of Agonists or Antagonists of the Invention***

##### **Astrocyte and Neuronal Assays.**

[01071] Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

[01072] Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two

responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

**Fibroblast and endothelial cell assays.**

[01073] Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

[01074] Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

**Parkinson Models.**

[01075] The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP<sup>+</sup>) and released. Subsequently, MPP<sup>+</sup> is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP<sup>+</sup> is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

[01076] It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

[01077] Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

[01078] Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

[01079] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 25: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells***

[01080] On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

[01081] An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cells indicates that the compound of the invention inhibits vascular endothelial cells.

[01082] The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

### ***Example 26: Rat Corneal Wound Healing Model***

[01083] This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm from the edge of the eye).

Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

[01084] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### ***Example 27: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing***

#### ***Models***

##### ***Diabetic db+/db+ Mouse Model.***

[01085] To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. et al., J. Surg. Res. 52:389 (1992); Greenhalgh, D.G. et al., Am. J. Pathol. 136:1235 (1990)).

[01086] The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single

autosomal recessive mutation on chromosome 4 (db+) (Coleman et al. Proc. Natl. Acad. Sci. USA 77:283-293. (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel et al., J. Immunol. 120:1375 (1978); Debray-Sachs, M. et al., Clin. Exp. Immunol. 51(1):1-7 (1983); Leiter et al., Am. J. of Pathol. 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. et al., Exp. Neurol. 83(2):221-232 (1984); Robertson et al., Diabetes 29(1):60-67 (1980); Giacomelli et al., Lab Invest. 40(4):460-473 (1979); Coleman, D.L., Diabetes 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel et al., J. Immunol. 120:1375-1377 (1978)).

[01087] The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, et al., Am. J. of Pathol. 136:1235-1246 (1990)).

[01088] Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[01089] Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., J. Exp. Med. 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is



given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[01090] Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[01091] An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[01092] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[01093] Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

[01094] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

[01095] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-

epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

[01096] Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

[01097] Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

[01098] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

#### *Steroid Impaired Rat Model*

[01099] The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet al., J. Immunol. 115: 476-481 (1975); Werb et al., J. Exp. Med. 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert et al., An. Intern. Med. 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck et al., Growth Factors. 5: 295-304 (1991); Haynes et al., J. Clin. Invest. 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and

Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce et al., Proc. Natl. Acad. Sci. USA 86: 2229-2233 (1989)).

[01100] To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

[01101] Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[01102] The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[01103] Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[01104] The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

- [01105] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.
- [01106] Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.
- [01107] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:
- [01108] 
$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$
- [01109] Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.
- [01110] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.
- [01111] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

### *Example 28: Lymphadema Animal Model*

[01112] The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

[01113] Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

[01114] Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

[01115] Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

[01116] Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ

Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

[01117] To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect of plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

[01118] Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people and those 2 readings are averaged. Readings are taken from both control and edematous limbs.

[01119] Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), and both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level, then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

[01120] Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and  $\text{Ca}^{2+}$  comparison.

[01121] Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

[01122] Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

[01123] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 29: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention***

[01124] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[01125] Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

[01126] The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

[01127] To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>. HUVECs are seeded in 96-

well plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

[01128] Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90  $\mu$ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ ) is added to each well. Plates are held at 4°C for 30 min.

[01129] Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10  $\mu$ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

[01130] Then add 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer:  $1:5,000$  ( $10^0$ )  $> 10^{-0.5}$   $> 10^{-1}$   $> 10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.



- [01131] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

***Example 30: Production Of Polypeptide of the Invention For High-Throughput Screening Assays***

- [01132] The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 32-41.

- [01133] First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

- [01134] Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

- [01135] The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well.

As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

[01136] Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

[01137] While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of

Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

[01138] The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

[01139] On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 32-39.

[01140] It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

### ***Example 31: Construction of GAS Reporter Construct***

[01141] One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-

sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

[01142] GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

[01143] The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

[01144] The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:2)).

[01145] Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

[01146] Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using

- GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

<u>JAKs</u>	<u>STATS</u>		<u>GAS(elements) or ISRE</u>			
<u>Ligand</u>		<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	
<u>IFN family</u>						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g (IRF1>Lys6>IFP)		+	+	-	1	GAS
IL-10	+	?	?	-	1,3	
<u>gp130 family</u>						
IL-6 (Pleiotropic) (IRF1>Lys6>IFP)	+	+	+	?	1,3	GAS
IL-11(Pleiotropic)	?	+	?	?	1,3	
OnM(Pleiotropic)	?	+	+	?	1,3	
LIF(Pleiotropic)	?	+	+	?	1,3	
CNTF(Pleiotropic)	-/+	+	+	?	1,3	
G-CSF(Pleiotropic)	?	+	?	?	1,3	
IL-12(Pleiotropic)	+	-	+	+	1,3	
<u>g-C family</u>						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid) >>Ly6)(IgH)	-	+	-	+	6	GAS(IRF1=IFP)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>						
IL-3 (myeloid) (IRF1>IFP>>Ly6)	-	-	+	-	5	GAS
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-
CAS>IRF1=IFP>>Ly6)						
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

[01147] To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 32-33, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO: 3)

[01148] The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 4)

[01149] PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGC  
CCCTAACTCCGCCCATCCCGCCCCCTAACTCCGCCCAGTTCCGCCCATTCTCC  
GCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTC  
GGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGG  
CTTTTGCAAAAAGCTT:3' (SEQ ID NO: 5)

[01150] With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be used instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

[01151] The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[01152] Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 32-33.

[01153] Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 34 and 35. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

### ***Example 32: High-Throughput Screening Assay for T-cell Activity.***

[01154] The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 31. Thus, factors that increase SEAP



activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

[01155] Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

[01156] Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

[01157] During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

[01158] The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 30.

[01159] On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

- [01160] Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).
- [01161] After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.
- [01162] The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 36. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.
- [01163] As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.
- [01164] The above protocol may be used in the generation of both transient, as well as stable, transfected cells, which would be apparent to those of skill in the art.

***Example 33: High-Throughput Screening Assay***  
***Identifying Myeloid Activity***

- [01165] The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 31. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

- [01166] To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 31, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.
- [01167] Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37 degrees C for 45 min.
- [01168] Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.
- [01169] The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.
- [01170] These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).
- [01171] Add 50 ul of the supernatant prepared by the protocol described in Example 30. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 36.

***Example 34: High-Throughput Screening Assay***  
***Identifying Neuronal Activity.***

- [01172] When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes,

EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

[01173] Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

[01174] The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO: 7)

[01175] Using the GAS:SEAP/Neo vector produced in Example 31, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

[01176] To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

[01177] PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is

done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

[01178] Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 30. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

[01179] To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

[01180] The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

[01181] Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 30, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 36.

### ***Example 35: High-Throughput Screening Assay for T-cell Activity***

[01182] NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of

apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

[01183] In non-stimulated conditions, NF- KB is retained in the cytoplasm with I- KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

[01184] Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 30. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

[01185] To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO: 8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO: 9)

[01186] The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 4)

[01187] PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA

CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTAT  
TCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGC  
TT:3' (SEQ ID NO: 10)

[01188] Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[01189] In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

[01190] Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 32. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 32. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

### *Example 36: Assay for SEAP Activity*

[01191] As a reporter molecule for the assays described in Examples 32-35, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

[01192] Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

[01193] Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the

Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

[01194] Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

**Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25



36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

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***Example 37: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability***

[01195] Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

[01196] The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

[01197] For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20

hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

[01198] A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

[01199] For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

[01200] For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

[01201] To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

### ***Example 38: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity***

[01202] The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth

factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

[01203] Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

[01204] Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

[01205] Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

[01206] To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyn plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 30, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

[01207] Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

[01208] Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

[01209] The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate (1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

- [01210] The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.
- [01211] Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase (anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.
- [01212] Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

***Example 39: High-Throughput Screening Assay Identifying  
Phosphorylation Activity***

- [01213] As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 38, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.
- [01214] Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against

Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

[01215] A431 cells are seeded at 20,000/well in a 96-well Loprodyn filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 30 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

[01216] After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

***Example 40: Assay for the Stimulation of Bone Marrow  
CD34+ Cell Proliferation***

[01217] This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

[01218] It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the

presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

[01219] Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l of the supernatants prepared in Example 30 (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

[01220] Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60  $\mu$ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for

counting. The sealed plates are then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

[01221] The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

[01222] The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

#### ***Example 41: Assay for Extracellular Matrix Enhanced Cell Response (EMECR)***

[01223] The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

[01224] Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is



dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and are responsible for stimulating stem cell self-renewal have not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

[01225] Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 30), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernatants represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5%  $\text{CO}_2$ , 7%  $\text{O}_2$ , and 88%  $\text{N}_2$ ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

[01226] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

[01227] If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease"

sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

[01228] Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

[01229] Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

***Example 42: Human Dermal Fibroblast and Aortic  
Smooth Muscle Cell Proliferation***

[01230] The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

[01231] Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 $\mu$ g/ml Amphotericin B, 0.4% FBS. Incubate at 37 °C until day 2.

[01232] On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37 degrees C/5% CO<sub>2</sub> until day 5.

[01233] Transfer 60 $\mu$ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4 degrees C until Day 6 (for IL6 ELISA). To the remaining 100  $\mu$ l in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10 $\mu$ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

[01234] On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100  $\mu$ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

[01235] On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200  $\mu$ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50  $\mu$ l/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make

dilutions of IL-6 stock in media (30, 10, 3, 1; 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

[01236] Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100  $\mu$ l/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels.

[01237] Add 100  $\mu$ l/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

[01238] A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular agent (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular

adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

[01239] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

***Example 43: Cellular Adhesion Molecule (CAM) Expression  
on Endothelial Cells***

[01240] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[01241] Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h

(selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$ ) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100  $\mu$ l of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50  $\mu$ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

#### ***Example 44: Alamar Blue Endothelial Cells Proliferation Assay***

[01242] This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay

is prepared in EGM-2MV with 10 ng/ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

[01243] Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37degrees C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

[01244] Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form (i.e., stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity). The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

***Example 45: Detection of Inhibition of a Mixed Lymphocyte Reaction***

[01245] This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

[01246] Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

[01247] Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.



[01248] Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

[01249] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

#### *Example 46: Assays for Protease Activity*

[01250] The following assay may be used to assess protease activity of the polypeptides of the invention.

[01251] Gelatin and casein zymography are performed essentially as described (Heusen et al., Anal. Biochem., 102:196-202 (1980); Wilson et al., Journal of Urology, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelatin or casein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis appear as clear areas against the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

[01252] Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mM NaPO<sub>4</sub>, 1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

[01253] Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., Methods of Enzymatic Analysis, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, Applied Science, 251-317 (1983).

#### *Example 47: Identifying Serine Protease Substrate Specificity*

[01254] Methods known in the art or described herein may be used to determine the substrate specificity of the polypeptides of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

#### ***Example 48: Ligand Binding Assays***

[01255] The following assay may be used to assess ligand binding activity of the polypeptides of the invention.

[01256] Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for a polypeptide is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards its polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

#### ***Example 49: Functional Assay in *Xenopus* Oocytes***

[01257] Capped RNA transcripts from linearized plasmid templates encoding the polypeptides of the invention are synthesized *in vitro* with RNA polymerases in accordance with standard procedures. *In vitro* transcripts are suspended in water at a final concentration of 0.2 mg/ml. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocyte) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage

clamps are used to measure the currents from individual *Xenopus oocytes* in response to polypeptides and polypeptide agonist exposure. Recordings are made in  $\text{Ca}^{2+}$  free Barth's medium at room temperature. The *Xenopus* system can be used to screen known ligands and tissue/cell extracts for activating ligands.

#### ***Example 50: Microphysiometric Assays***

[01258] Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the activation of polypeptide which is coupled to an energy utilizing intracellular signaling pathway.

#### ***Example 51: Extract/Cell Supernatant Screening***

[01259] A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the polypeptides of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated and identified.

#### ***Example 52: Calcium and cAMP Functional Assays***

[01260] Seven transmembrane receptors which are expressed in HEK 293 cells have been shown to be coupled functionally to activation of PLC and calcium

mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM, range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

### *Example 53: ATP-binding assay*

[01261] The following assay may be used to assess ATP-binding activity of polypeptides of the invention.

[01262] ATP-binding activity of the polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenylyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (<sup>32</sup>P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing

ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the polypeptides.

### *Example 54: Small Molecule Screening*

[01263] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and polypeptide of the invention.

[01264] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the invention. These methods comprise contacting such an agent with a polypeptide of the invention or fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the invention.

[01265] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with polypeptides of the invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly

onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[01266] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### ***Example 55: Phosphorylation Assay***

[01267] In order to assay for phosphorylation activity of the polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled  $^{32}\text{P}$ -ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The polypeptides of the invention are incubated with the protein substrate,  $^{32}\text{P}$ -ATP, and a kinase buffer. The  $^{32}\text{P}$  incorporated into the substrate is then separated from free  $^{32}\text{P}$ -ATP by electrophoresis, and the incorporated  $^{32}\text{P}$  is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the polypeptides of the invention.

#### ***Example 56: Detection of Phosphorylation Activity (Activation) of the Polypeptides of the Invention in the Presence of Polypeptide Ligands***

[01268] Methods known in the art or described herein may be used to determine the phosphorylation activity of the polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in U.S. 5,817,471 (incorporated herein by reference).

***Example 57: Identification Of Signal Transduction Proteins That Interact With Polypeptides Of The Present Invention***

[01269] The purified polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled receptor PTK polypeptide is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, receptor PTK polypeptide is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the receptor PTK polypeptides, or specific phosphotyrosine-recognition domains thereof. The receptor PTK polypeptide interacting protein-complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

***Example 58: IL-6 Bioassay***

[01270] To test the proliferative effects of the polypeptides of the invention, the IL-6 Bioassay as described by Marz *et al.* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 95:3251-56 (1998), which is herein incorporated by reference). Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50  $\mu$ l, and 50  $\mu$ l of the IL-6-like polypeptide is added. After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are utilized. Enhanced proliferation in the test sample(s) relative to the negative control is indicative of proliferative effects mediated by polypeptides of the invention.

***Example 59: Support of Chicken Embryo Neuron Survival***

[01271] To test whether sympathetic neuronal cell viability is supported by polypeptides of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* is utilized (*Proc. Natl. Acad. Sci., U.S.A.*, 96:11458-63 (1998), which is herein incorporated by reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% CO<sub>2</sub> in the presence of different concentrations of the purified IL-6-like polypeptide, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mossmann, T., *J. Immunol. Methods*, 65:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the inventive purified IL-6-like polypeptide(s) to enhance the survival of neuronal cells.

***Example 60: Assay for Phosphatase Activity***

[01272] The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the polypeptides of the invention.

[01273] In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [<sup>32</sup>P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.



***Example 61: Interaction of Serine/Threonine  
Phosphatases with other Proteins***

[01274] The polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 60 are research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, labeled polypeptide(s) of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptide of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The polypeptides of the invention -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

***Example 62: Assaying for Heparanase Activity***

[01275] In order to assay for heparanase activity of the polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells ( $1 \times 10^6$  cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with  $^{35}\text{S}$ -labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at  $0.5 < K_{av} < 0.8$  (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the polypeptides of the invention in cleaving heparan

sulfate.

[01276]      *Example 63: Immobilization of biomolecules*

[01277]      This example provides a method for the stabilization of polypeptides of the invention in non-host cell lipid bilayer constructs (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of polypeptides of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular domain of the polypeptides of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of polypeptides of the invention in washed membranes is incubated with 20 mM NaIO<sub>4</sub> and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl<sub>2</sub>, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

*Example 64: TAQMAN*

[01278]      Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with DNase I (Life Technologies) to remove any contaminating genomic DNA before reverse transcription.) Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of Taqman Buffer A (Perkin-Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM MgCl<sub>2</sub>, 240 µM each dNTP, 0.4 units RNase inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05% gelatin, 0.3uM primers, 0.1uM probe, 0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units Superscript II reverse

transcriptase (Life Technologies). As a control for genomic contamination, parallel reactions are setup without reverse transcriptase. The relative abundance of (unknown) and 18S RNAs are assessed by using the Applied Biosystems Prism 7700 Sequence Detection System (Livak, K. J., Flood, S. J., Marmaro, J., Giusti, W. & Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are carried out at 48°C for 30 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1 min. Reactions are performed in triplicate.

[01279] Primers (f & r) and FRET probes sets are designed using Primer Express Software (Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-Elmer).

### *Example 65: Assays for Metalloproteinase Activity*

[01280] Metalloproteinases (EC 3.4.24.-) are peptide hydrolases which use metal ions, such as  $Zn^{2+}$ , as the catalytic mechanism. Metalloproteinase activity of polypeptides of the present invention can be assayed according to the following methods.

#### *Proteolysis of alpha-2-macroglobulin*

[01281] To confirm protease activity, purified polypeptides of the invention are mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml; Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM  $CaCl_2$ , 25  $\mu M$   $ZnCl_2$  and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

#### *Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases*

[01282] Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND  $\text{HgCl}_2$ ), peptide metalloproteinase inhibitors (TIMP-1 and TIMP-2), and commercial small molecule MMP inhibitors) are used to characterize the proteolytic activity of polypeptides of the invention. The three synthetic MMP inhibitors used are: MMP inhibitor I, [ $\text{IC}_{50} = 1.0 \mu\text{M}$  against MMP-1 and MMP-8;  $\text{IC}_{50} = 30 \mu\text{M}$  against MMP-9;  $\text{IC}_{50} = 150 \mu\text{M}$  against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [ $\text{IC}_{50} = 5 \mu\text{M}$  against MMP-3], and MMP-3 inhibitor II [ $\text{K}_i = 130 \text{ nM}$  against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with purified polypeptides of the invention ( $50 \mu\text{g/ml}$ ) in  $22.9 \mu\text{l}$  of 1x HEPES buffer ( $50 \text{ mM}$  HEPES, pH 7.5,  $0.2 \text{ M}$  NaCl,  $10 \text{ mM}$   $\text{CaCl}_2$ ,  $25 \mu\text{M}$   $\text{ZnCl}_2$  and  $0.05\%$  Brij-35) and incubated at room temperature ( $24^\circ\text{C}$ ) for 2-hr, then  $7.1 \mu\text{l}$  of substrate alpha-2-macroglobulin ( $0.2 \text{ unit/ml}$ ) is added and incubated at  $37^\circ\text{C}$  for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

*Synthetic Fluorogenic Peptide Substrates Cleavage Assay*

[01283] The substrate specificity for polypeptides of the invention with demonstrated metalloproteinase activity can be determined using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) converting enzyme (TACE). All the substrates are prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are  $50\text{-}500 \mu\text{M}$ . Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant temperature water bath. The excitation  $\lambda$  is  $328 \text{ nm}$  and the emission  $\lambda$  is  $393 \text{ nm}$ . Briefly, the assay is carried out by incubating  $176 \mu\text{l}$  1x HEPES buffer ( $0.2 \text{ M}$  NaCl,  $10 \text{ mM}$   $\text{CaCl}_2$ ,  $0.05\%$  Brij-35 and  $50 \text{ mM}$  HEPES, pH 7.5) with  $4 \mu\text{l}$  of substrate solution ( $50 \mu\text{M}$ ) at  $25^\circ\text{C}$  for 15 minutes, and then adding  $20 \mu\text{l}$  of a purified polypeptide of the invention into the assay cuvet. The final concentration of substrate is  $1 \mu\text{M}$ . Initial hydrolysis rates are monitored for 30-min.

***Example 66: Characterization of the cDNA contained in a deposited plasmid***

[01284] The size of the cDNA insert contained in a deposited plasmid may be routinely determined using techniques known in the art, such as PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the cDNA sequence. For example, two primers of 17-30 nucleotides derived from each end of the cDNA (i.e., hybridizable to the absolute 5' nucleotide or the 3' nucleotide end of the sequence of SEQ ID NO:X, respectively) are synthesized and used to amplify the cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[01285] Use of the above methodologies and/or other methodologies known in the art generates fragments from the clone corresponding to the approximate fragments described in Table 8, below. Accordingly, Table 8 provides a physical characterization of certain clones encompassed by the invention. The first column provides the unique clone identifier, "Clone ID NO:Z," for cDNA clones of the invention, as described in Table 1A. The second column provides the approximate size of the cDNA insert contained in the corresponding cDNA clone.

**TABLE 8**

Clone ID NO:Z	cDNA Insert Size:
-----	

HUFDB55	2200
HUVDJ10	2000
HUFAJ16	800
HTPDV49	2600
HROAL96	700
HLQBS59	1300
HGBGL83	700

[01286] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[01287] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. In addition, the CD-R copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. The specification and Sequence Listing of each of the following U.S. applications are herein incorporated by reference in their entirety: Application No. 60/179,065, filed on 31-Jan-2000; Application No. 60/180,628, filed on 04-Feb-2000; Application No. 60/214,886, filed on 28-Jun-2000; Application No. 60/217,487, filed on 11-Jul-2000; Application No. 60/225,758, filed on 14-Aug-2000; Application No. 60/220,963, filed on 26-Jul-2000; Application No. 60/217,496, filed on 11-Jul-2000; Application No. 60/225,447, filed on 14-Aug-2000; Application No. 60/218,290, filed on 14-Jul-2000; Application No. 60/225,757, filed on 14-Aug-2000; Application No. 60/226,868, filed on 22-Aug-2000; Application No. 60/216,647, filed on 07-Jul-2000; Application No. 60/225,267, filed on 14-Aug-2000; Application No. 60/216,880, filed on 07-Jul-2000; Application No. 60/225,270, filed on 14-Aug-2000; Application No. 60/251,869, filed on 08-Dec-2000; Application No.

60/235,834, filed on 27-Sep-2000; Application No. 60/234,274, filed on 21-Sep-2000; Application No. 60/234,223, filed on 21-Sep-2000; Application No. 60/228,924, filed on 30-Aug-2000; Application No. 60/224,518, filed on 14-Aug-2000; Application No. 60/236,369, filed on 29-Sep-2000; Application No. 60/224,519, filed on 14-Aug-2000; Application No. 60/220,964, filed on 26-Jul-2000; Application No. 60/241,809, filed on 20-Oct-2000; Application No. 60/249,299, filed on 17-Nov-2000; Application No. 60/236,327, filed on 29-Sep-2000; Application No. 60/241,785, filed on 20-Oct-2000; Application No. 60/244,617, filed on 01-Nov-2000; Application No. 60/225,268, filed on 14-Aug-2000; Application No. 60/236,368, filed on 29-Sep-2000; Application No. 60/251,856, filed on 08-Dec-2000; Application No. 60/251,868, filed on 08-Dec-2000; Application No. 60/229,344, filed on 01-Sep-2000; Application No. 60/234,997, filed on 25-Sep-2000; Application No. 60/229,343, filed on 01-Sep-2000; Application No. 60/229,345, filed on 01-Sep-2000; Application No. 60/229,287, filed on 01-Sep-2000; Application No. 60/229,513, filed on 05-Sep-2000; Application No. 60/231,413, filed on 08-Sep-2000; Application No. 60/229,509, filed on 05-Sep-2000; Application No. 60/236,367, filed on 29-Sep-2000; Application No. 60/237,039, filed on 02-Oct-2000; Application No. 60/237,038, filed on 02-Oct-2000; Application No. 60/236,370, filed on 29-Sep-2000; Application No. 60/236,802, filed on 02-Oct-2000; Application No. 60/237,037, filed on 02-Oct-2000; Application No. 60/237,040, filed on 02-Oct-2000; Application No. 60/240,960, filed on 20-Oct-2000; Application No. 60/239,935, filed on 13-Oct-2000; Application No. 60/239,937, filed on 13-Oct-2000; Application No. 60/241,787, filed on 20-Oct-2000; Application No. 60/246,474, filed on 08-Nov-2000; Application No. 60/246,532, filed on 08-Nov-2000; Application No. 60/249,216, filed on 17-Nov-2000; Application No. 60/249,210, filed on 17-Nov-2000; Application No. 60/226,681, filed on 22-Aug-2000; Application No. 60/225,759, filed on 14-Aug-2000; Application No. 60/225,213, filed on 14-Aug-2000; Application No. 60/227,182, filed on 22-Aug-2000; Application No. 60/225,214, filed on 14-Aug-2000; Application No. 60/235,836, filed on 27-Sep-2000; Application No. 60/230,438, filed on 06-Sep-2000; Application No. 60/215,135, filed on 30-Jun-2000; Application No. 60/225,266, filed on 14-Aug-2000; Application No. 60/249,218, filed on 17-Nov-2000; Application No. 60/249,208, filed on 17-Nov-2000; Application No.

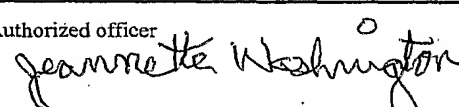
60/249,213, filed on 17-Nov-2000; Application No. 60/249,212, filed on 17-Nov-2000; Application No. 60/249,207, filed on 17-Nov-2000; Application No. 60/249,245, filed on 17-Nov-2000; Application No. 60/249,244, filed on 17-Nov-2000; Application No. 60/249,217, filed on 17-Nov-2000; Application No. 60/249,211, filed on 17-Nov-2000; Application No. 60/249,215, filed on 17-Nov-2000; Application No. 60/249,264, filed on 17-Nov-2000; Application No. 60/249,214, filed on 17-Nov-2000; Application No. 60/249,297, filed on 17-Nov-2000; Application No. 60/232,400, filed on 14-Sep-2000; Application No. 60/231,242, filed on 08-Sep-2000; Application No. 60/232,081, filed on 08-Sep-2000; Application No. 60/232,080, filed on 08-Sep-2000; Application No. 60/231,414, filed on 08-Sep-2000; Application No. 60/231,244, filed on 08-Sep-2000; Application No. 60/233,064, filed on 14-Sep-2000; Application No. 60/233,063, filed on 14-Sep-2000; Application No. 60/232,397, filed on 14-Sep-2000; Application No. 60/232,399, filed on 14-Sep-2000; Application No. 60/232,401, filed on 14-Sep-2000; Application No. 60/241,808, filed on 20-Oct-2000; Application No. 60/241,826, filed on 20-Oct-2000; Application No. 60/241,786, filed on 20-Oct-2000; Application No. 60/241,221, filed on 20-Oct-2000; Application No. 60/246,475, filed on 08-Nov-2000; Application No. 60/231,243, filed on 08-Sep-2000; Application No. 60/233,065, filed on 14-Sep-2000; Application No. 60/232,398, filed on 14-Sep-2000; Application No. 60/234,998, filed on 25-Sep-2000; Application No. 60/246,477, filed on 08-Nov-2000; Application No. 60/246,528, filed on 08-Nov-2000; Application No. 60/246,525, filed on 08-Nov-2000; Application No. 60/246,476, filed on 08-Nov-2000; Application No. 60/246,526, filed on 08-Nov-2000; Application No. PT172, filed on 17-Nov-2000; Application No. 60/246,527, filed on 08-Nov-2000; Application No. 60/246,523, filed on 08-Nov-2000; Application No. 60/246,524, filed on 08-Nov-2000; Application No. 60/246,478, filed on 08-Nov-2000; Application No. 60/246,609, filed on 08-Nov-2000; Application No. 60/246,613, filed on 08-Nov-2000; Application No. 60/249,300, filed on 17-Nov-2000; Application No. 60/249,265, filed on 17-Nov-2000; Application No. 60/246,610, filed on 08-Nov-2000; Application No. 60/246,611, filed on 08-Nov-2000; Application No. 60/230,437, filed on 06-Sep-2000; Application No. 60/251,990, filed on 08-Dec-2000; Application No. 60/251,988, filed



on 05-Dec-2000; Application No. 60/251,030, filed on 05-Dec-2000; Application No. 60/251,479, filed on 06-Dec-2000; Application No. PJ005, filed on 05-Dec-2000; Application No. PJ006, filed on 01-Dec-2000; Application No. 60/251,989, filed on 08-Dec-2000; Application No. 60/250,391, filed on 01-Dec-2000; and Application No. 60/254,097, filed on 11-Dec-2000.

[01288] Moreover, the microfiche copy and the corresponding computer readable form of the Sequence Listing of U.S. Application Serial No. 60/179,065, and the hard copy of and the corresponding computer readable form of the Sequence Listing of U.S. Application Serial No. 60/180,628 are also incorporated herein by reference in their entireties.

<b>INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL</b> (PCT Rule 13bis)					
A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.					
<b>B. IDENTIFICATION OF DEPOSIT</b> <span style="float: right;">Further deposits are identified on an additional sheet <input checked="" type="checkbox"/></span>					
Name of depositary institution: American Type Culture Collection					
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America					
Date of deposit    May 20, 1997			Accession Number    209059		
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>					
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)					
Europe In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). <div style="text-align: right;">Continued on additional sheets</div>					
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)					
The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")					
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<b>INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL</b>  <b>(PCT Rule 13bis)</b>			
<b>A.</b> The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.			
<b>B. IDENTIFICATION OF DEPOSIT</b>		Further deposits are identified on an additional sheet <u>  </u>	
Name of depositary institution: American Type Culture Collection			
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America			
Date of deposit    May 20, 1997 Accession Number    209060			
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <u>  </u>			
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)			
Europe In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). <div style="text-align: right;">Continued on additional sheets</div>			
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)			
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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209061

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209062

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209063

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe.

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209064

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209065

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

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Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
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United States of America

Date of deposit May 20, 1997

Accession Number 209066

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209067

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209068

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

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A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

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Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit May 20, 1997

Accession Number 209069

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

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OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

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Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit January 12, 1998

Accession Number 209579

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

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**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209

United States of America

Date of deposit January 12, 1998

Accession Number 209578

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (*including postal code and country*)

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit July 16, 1998

Accession Number 203067

**C. ADDITIONAL INDICATIONS** (*leave blank if not applicable*)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (*if the indications are not for all designated States*)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (*leave blank if not applicable*)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit July 16, 1998

Accession Number 203068

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit February 1, 1999

Accession Number 203609

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

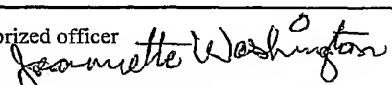
**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit February 1, 1999

Accession Number 203610

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

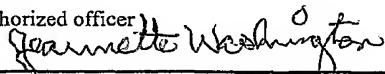
**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit November 17, 1998

Accession Number 203485

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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*Jeanette Washington*

Authorized officer

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

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Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit June 18, 1999

Accession Number PTA-252

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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<b>INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL</b>  (PCT Rule 13bis)			
A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6:			
<b>B. IDENTIFICATION OF DEPOSIT</b>		Further deposits are identified on an additional sheet <input checked="" type="checkbox"/>	
Name of depositary institution: American Type Culture Collection			
Address of depositary institution <i>(including postal code and country)</i> 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America			
Date of deposit     June 18, 1999		Accession Number     PTA-253	
<b>C. ADDITIONAL INDICATIONS</b> <i>(leave blank if not applicable)</i>		This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> <i>(if the indications are not for all designated States)</i>			
Europe In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC). <div style="text-align: right;">Continued on additional sheets</div>			
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> <i>(leave blank if not applicable)</i>			
The indications listed below will be submitted to the international Bureau later <i>(specify the general nature of the indications e.g., "Accession Number of Deposit")</i>			
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Authorized officer <i>Jeannette Washington</i>		Authorized officer	

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Table 6.

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit December 22, 1999

Accession Number PTA-1081

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).  
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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at pages 23-24, paragraph [054].

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country)  
10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit October 5, 2000

Accession Number PTA-2574

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at pages 23-24, paragraph [054].

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit    October 5, 2000

Accession Number    PTA-2575

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at pages 23-24, paragraph [054].

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209

United States of America

Date of deposit January 5, 2001

Accession Number (HGS reference code TS-1)

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at pages 23-24, paragraph [054]..

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution (including postal code and country).

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit January 5, 2001

Accession Number (HGS reference code TS-2)

**C. ADDITIONAL INDICATIONS** (leave blank if not applicable)

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** (if the indications are not for all designated States)

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** (leave blank if not applicable)

The indications listed below will be submitted to the international Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")

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Authorized officer <i>James H. Washington</i>			Authorized officer		

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at pages 23-24, paragraph [054].

**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☒

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit: January 5, 2001

Accession Number (HGS reference code AC-1)

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

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**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM  
OR OTHER BIOLOGICAL MATERIAL**

(PCT Rule 13bis)

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**B. IDENTIFICATION OF DEPOSIT**

Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*

10801 University Boulevard  
Manassas, Virginia 20110-2209  
United States of America

Date of deposit January 5, 2001

Accession Number (HGS reference code AC-2)

**C. ADDITIONAL INDICATIONS** *(leave blank if not applicable)*

This information is continued on an additional sheet ☐

**D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE** *(if the indications are not for all designated States)*

Europe

In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

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**E. SEPARATE FURNISHING OF INDICATIONS** *(leave blank if not applicable)*

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Authorized officer <i>Joannette Washington</i>			Authorized officer		

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ATCC Deposit No.: 209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069, 209579, 209578, 203067, 203068, 203609, 203610, 203485, PTA-252, PTA-253, PTA-1081, PTA-2574, PTA-2575, TS-1, TS-2, AC-1, AC-2

#### CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner; the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

#### NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

#### AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

#### FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: 209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069, 209579, 209578, 203067, 203068, 203609, 203610, 203485, PTA-252, PTA-253, PTA-1081, PTA-2574, PTA-2575, TS-1, TS-2, AC-1, AC-2

#### UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made

available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence contained in Clone ID NO:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X;

(f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(g) a polynucleotide which is a variant of SEQ ID NO:X;

(h) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.



2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.
3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X.
4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence contained in cDNA Clone ID NO:Z, which is hybridizable to SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence contained in cDNA Clone ID NO:Z;
  - (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence contained in cDNA Clone ID NO:Z, having biological activity;
  - (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence contained in cDNA Clone ID NO:Z;
  - (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence contained in cDNA Clone ID NO:Z;
  - (e) a full length protein of SEQ ID NO:Y or the encoded sequence contained in cDNA Clone ID NO:Z;
  - (f) a variant of SEQ ID NO:Y;
  - (g) an allelic variant of SEQ ID NO:Y; or
  - (h) a species homologue of the SEQ ID NO:Y.
12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
15. A method of making an isolated polypeptide comprising:
- (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and
  - (b) recovering said polypeptide.
16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

(c) detecting an activity in a biological assay; and

(d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.
24. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11.